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PSYCHOPHARMACOLOGIA

SPRINGER-VERLAG / BERLIN · GÖTTINGEN · HEIDELBERG

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Die Forschung über die Wirkungen und Wirkungsweisen psychotroper Substanzen hat in den letzten Jahren einen unerhörten Aufschwung genommen. Was vordem nur ein erwünschtes Ziel war, ist zu einer neuen Wissenschaft geworden: Psychopharmakologie. Da eine fruchtbare Analyse und Synthese ihrer Probleme nur durch Zusammenarbeit aller Grundfächer (Pharmakologie, Neurochemie, Neurophysiologie, Neurologie, Psychologie und Psychiatrie) möglich wird, ist die Psychopharmakologie eine verbindende, integrierende Forschungsdisziplin. Die ständig anwachsende Literatur dieses komplexen Arbeitsgebietes ist jedoch bisher zwangsläufig über zahlreiche Zeitschriften verstreut, da es bis heute kein Spezialorgan gab, das sich ausschließlich der Psychopharmakologie widmet. Diesem dringenden Bedürfnis zu begegnen, hat sich eine Gruppe von Vertretern der verschiedenen Arbeitsrichtungen der Psychopharmakologie entschlossen, eine neue Zeitschrift „Psychopharmacologia" zu gründen. In ihr sollen die bedeutenden Fortschritte dieses Arbeitsgebietes durch Veröffentlichung experimenteller und klinischer Originalarbeiten, Übersichten der neuesten Literatur sowie kurzer Originalmitteilungen zusammengefaßt werden.

Recent years have witnessed an unprecedented advance in research on the action and effects of psychotropic drugs, and what, formerly, was just a distant goal, has now evolved into a new branch of science: psychopharmacology. As, however, any fruitful analysis and synthesis of its problems can only be attained with the aid of the complete scale of basic sciences (pharmacology, neurochemistry, neurophysiology, neurology, psychology and psychiatry), psychopharmacology constitutes an integrating discipline of research. Owing to the lack of an organ devoted especially to psychopharmacology, the constantly increasing literature pertaining to this complex field of activity has hitherto of necessity been scattered among various periodicals. In order to overcome this drawback, a group of representatives of the various psychopharmacologic sections have engaged in editing a journal, "Psychopharmacologia", in which the publication of original experimental and clinical papers, reviews of recent literature and short original notices will provide a comprehensive survey of the important progress which is being actually achieved in this field of science.

Ces dernières années ont vu un développement sans précédent dans la recherche des effets et du mode d'action des substances psychotropes sur le «Comportement» et ont fait naître une nouvelle science: la Psychopharmacologie. Comme ces problèmes ne peuvent être résolus que par la collaboration des disciplines de base telles que la pharmacologie, la neurochimie, la neurophysiologie, la psychologie et la psychiatrie, la psychopharmacologie est devenue un champ de recherche de première importance. Cependant la littérature toujours croissante en ce domaine de recherche est forcément disséminée dans de nombreux périodiques, puisqu'il n'existe pas encore de journal exclusivement consacré à la psychopharmacologie. Pour répondre à ce pressant besoin un groupe de représentants des diverses disciplines de la psychopharmacologie s'est mis en devoir de rédiger un nouveau journal dans lequel seraient rassemblés les progrès importants de ce domaine, par la publication d'ouvrages originaux expérimentaux et cliniques, ainsi que des rapports sur des questions actuelles.

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Psychopharmacologia

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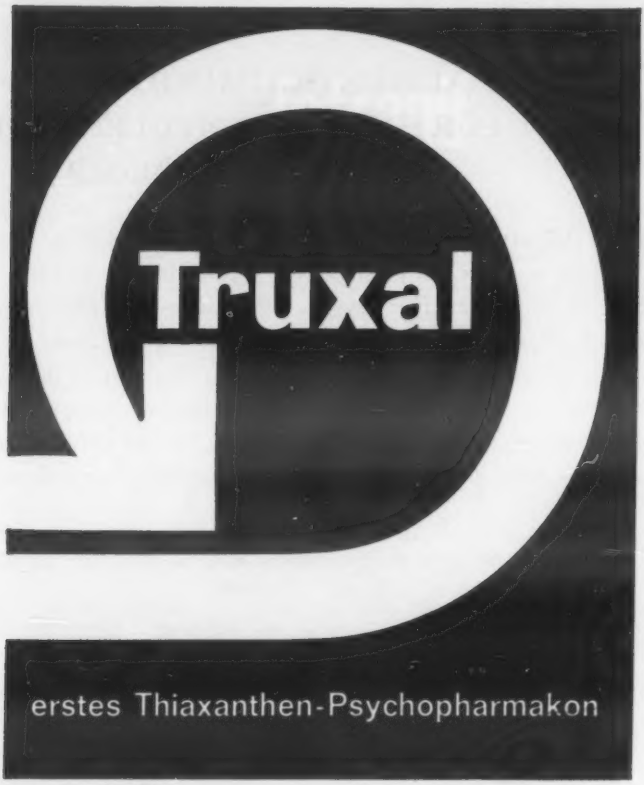

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Psychopharmacologia 1, 261—279 (1960)

Reviews · Übersichtsartikel · Revues générales

From the Washington School of Psychiatry, Washington 9, D.C.

Language and Psychopharmacology*

By

EDWIN A. WEINSTEIN

(Received March 25, 1960)

The subject of language is not ordinarily thought of as relevant to psychopharmacology which deals with biochemical processes and physiological and psychological phenomena. Yet, the study of the effects of drugs upon human behavior involves certain hypotheses about the relationship of language to the other functions of the brain. While an observer may be quite unaware that he has made any such a priori formulations, they nevertheless in good part determine not only what he deduces from his data but the selection and classification of such data. Psychiatrists for the most part have not been concerned with the organization and patterning mechanisms of language itself, apart from studies of aphasia. Although "organic" psychiatrists differ in many respects from "dynamic" ones, they both tend to equate symbolic patterns with psycho-physiological entities. Thus the verbal, vocal and gestural components of euphoric and paranoid behavior are generally taken to be the external manifestations of separate physiological processes or more basic psycho-dynamic mechanisms. Similarly, changes in sexual behavior occurring in patients with brain injuries or mental illnesses are usually considered to be expressions of "loss of ethical sense" or instinctive or libidinal drives. A delusion is defined as a disturbance of cognition or regarded as a manifestation of the release of hitherto repressed motives. In Freudian psychiatry, symbols are regarded as evidences of repression standing for things that are hidden. Aspects of symbolic processes such as condensation, displacement and projection are considered as evidences of repression. In the more recent literature the importance of language as a defense mechanism has been recognized but symbols still tend to be thought of in terms of the release of repressions.

The purpose of this paper is to present other views of symbolic behavior and to consider their relevance to psychopharmacology, to describe clinical phenomena associated with alterations in brain function in terms of symbolic organization and to indicate the uses of the study of language as a measure of altered brain function and behavioral change.

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Concepts of Language

The ideas of language that will be presented are drawn particularly from the writers of the symbolic interactionist school, notably G. H. MEAD, EDWARD SAPIR and BENJAMIN WHORF. While language is based on the ability to perceive selectively and generalize from among the details of situations, symbols cannot be equated with individual events of the physical world, whether within or without the body. Rather, what we see, hear and feel is a product of an interaction in the environment. Symbols take on form and meaning not through the intrinsic properties of the stimuli but by reason of the place of elements in a total pattern of relatedness. WHORF comments that the concept "blue" could have no meaning in a world where everything was blue. We hear the melody rather than the individual notes and a tune played in a different key sounds the same provided the notes bear the same temporal and spatial relationship to one another. An action cannot be meaningfully described as the sum of its neuro-muscular components but only as it fits into some program. Thus if one takes a "step" this must be defined in terms of its being directed and the end state to be reached.

While symbolic patterns are made up of motor and perceptual elements, symbolic behavior is differentiated from more "physiological" processes by the context in which it occurs and its socially patterned character. SKINNER defines verbal behavior as behavior reinforced through the mediation of other persons. In a physiological sense the blink of an eye is a means of lubricating the cornea and removing foreign bodies while as an element of a social pattern, it may communicate certain attitudes and feelings. The meaning of the act has little or nothing to do with the physiology of ocular movements. Language may be defined as a system of arbitrarily chosen symbols by which members of a society interact in terms of their culture. The designation "arbitrary" is used by the linguist because for him an event or an object like a chair might be called by any other name. Also a chair cannot be defined in terms only of its physical properties and functions. Chairs may be made up of various materials, different shapes and sizes and one may sit on a stool, bench or couch. While what we call a chair and feel is a chair depends on a certain spatial relationship among component parts, the designation also must fit a socially determined classification. Thus a "chair" up against a bar in a cocktail lounge becomes a stool or if it is on a dais in court it is a throne. Such distinctions are learned effortlessly by members of the social group. SAPIR suggests that even our "ohs" and "ahs" are not expressions of instincts and reflexes but are socially learned forms of language.

For the speakers of a language, however, symbols are not arbitrary but "natural" and by and large things are felt to be what they are called.

A rose by any other name would not smell as sweetly and a word like "juicy" practically exudes "juiciness", while one like "fracture" almost sounds like something breaking. Yet speakers of another language may get the same feeling from other designations. The *feeling* that things are what they are, the sense of identity, are derived through social transactions in a particular cultural group. Thus children learn to talk through an interaction in their environment of which they are unaware. A child uses intricate grammatical constructions and puts words in their proper context without any conception of the rules of syntax. An infant forms more or less unintelligible sounds like "ga" and "da". The adult responds to only some of these and they come to have meaning to the child in the context of the interpersonal situation. When a parent attends to the "ga" and to certain facial grimaces and types of breathing rather than to the glubs, snorts, sniffs and other facial-lingual-respiratory synkinesias, then "ga" has become a word and the facial movement has evolved into a smile. Yet "ga" refers not so much to a thing or act but a situation. When a child says he is "tired" this is not simply the verbal manifestation of a physiologically measurable state. Rather it is the product of an interaction involving his experience in situations where Mother has said she is tired and his expectation of the events that may follow such a statement. Further, the very language that he uses is a factor in determining the quality of the feeling of being "tired". SAPIR states:

"Even comparatively simple acts of perception are very much more at the mercy of social patterns called words than we might suppose. If one draws some dozen lines, for instance, of different shapes, one perceives them as divisible into such categories as "straight", "crooked", "curved", "zigzag" because of the classificatory suggestiveness of the linguistic terms themselves. We see and hear and otherwise experience very largely as we do because the language habits of our community predispose certain choices of interpretation".

The SAPIR-WHORF hypothesis, that the forms of language heuristically determine for us certain modes of observation and interpretation, has become of increasing importance to anthropologists and other social scientists. The material on which the ideas are based were taken largely from studies of the rather exotic North American Indian languages. It was found that in these languages concepts were formed and ideas communicated in a grammatical structure far different from those of the Indo-European languages. Yet the Indians, like the speakers of any language felt that they were reporting the events of the world in the only way in which they could be accurately represented. For example, in English we designate past, present and future by the use of three tenses of verbs[1]. Some Indian languages, however, do not have such

[1] Dr. GEORGE TRAGER in a personal communication states that English has only two tenses, present and past, but many "modes" as present future *will go*, past future *would go*, present potential *can go*, past potential *could go*, etc.

built-in verb forms to indicate past, present and future. Instead the verb suffix may give the relationship of the speaker to the event. Thus if it has rained, the verb form tells whether the speaker has seen it with his own eyes, or whether he has seen evidence such as a footprint or whether it is something that he has been told. The date of the event may be conveyed implicitly in the situation or may be indicated by a qualifying statement. In English, "fist" is a noun, while in Hopi it is a verb. WHORF believed that European languages imaginatively concretize time in spatial metaphors so that temporal units in their linguistic form are placed in the same category as "things". He suggests these "background phenomena" of language have profoundly influenced our space-time-matter classification of the universe. We use certain grammatical and linguistic forms not because they are actually necessary for the designation of reality but because we *feel* that they are. SAPIR comments that we could say "two house" just as well as "two houses" and probably no high school French student can understand why he must learn to classify the environment in terms of gender. Yet such redundancies of language operating out of the awareness of a native speaker shape his view of reality.

SAPIR has suggested a division of symbols into two groups, referential and experiential which may serve to illustrate some concepts of interaction. Referential symbols pertain to universally agreed upon systems of designation and communication such as letters, numbers, blueprints, flag-signalling devices and the Morse code. Experiential symbols on the other hand involve more personalized feelings and emotions. Included in this class would be prayers, poetic expressions, slogans, rituals, dances and many gestures. KENNETH BURKE has given a similar classification into semantic and poetic forms. Actually, it is difficult to find purely referential or experiential forms as most symbols have aspects of either mode. For example a trademark both identifies an article as the product of a maker and also expresses a feeling of tradition and pride in the making. The uniform and insignia of an organization serve not only to denote rank and the fact of membership but feelings of belonging and identity. Experiential symbols are more apt to refer to situations and systems of relationships than to "things". They tend, too, to transcend what are considered individual feelings. While a prayer may, in a referential sense, be regarded as a communication with the Deity or as an expression of love, fear or awe, yet the meaning and even the quality of the feeling derive to a great extent from the speaker's relatedness in the group. One is generally quite unaware of such a relatedness but senses the quality of the feeling as residing in the individual or the object. Thus one feels holy or regards sacredness as intrinsic to another person or object such as a relic.

The term "level of interaction in the environment" refers to the place of the symbol along a referential-experiential scale. It involves the classification of the environment, the diversity of patterns in which symbolic elements are integrated ,the facility with which one may shift from one pattern to another and the degree of awareness of the interaction. Thus certain forms of humor include the use of a symbolic element in several patterns, a shift between referential and experiential levels and an awareness of the interaction shown usually in "seeing the joke". A much less complex interaction would occur in a state of panic where the environment would be rigidly structured into what was felt as safe and what was felt as dangerous and the individual, quite unaware of the interaction, would regard the qualities of safety and danger as residing wholly in the outside environment.

Language is a social process and the units of symbolic behavior are to a large degree definable only in units of social interaction. It is for this reason that it has been so difficult to equate such phenomena as euphoric and paranoid behavior, delusions and hallucinations with physiological processes and psychological mechanisms. We recently made an investigation of the effect of brain lesions on overt sexual behavior (WEINSTEIN and KAHN, 1960). Although there was universal agreement among the staff of observers as to which patients showed it, the problem of definition of abnormal sexual behavior arose. Thus flirtatiousness could not in itself be considered aberrant. If a patient exposed himself, the question of whether he did so because he was unaware that he had kicked off the covers came up. The husband of one patient remarked that he was not surprised that she told off-color stories but that she related them to people whom she did not know. It became evident that the "sexual" quality of the behavior came not only from its intrinsic properties but from an interaction involving the background of social convention, the interpersonal situation and the observer's own "sexual" feelings. Similarly euphoric and paranoid behavior may be generally distinguished without difficulty. We consider euphoria as characterized by laughing, smiling, joking and verbal expressions of happiness and well being. Paranoid behavior consists of verbal and gestural expressions of anger, fear and threats. But a "happy" smile may be difficult to describe in contrast to a "sarcastic" one and paranoid ideas may be accompanied by a laugh. The same verbal content can be used in an euphoric and paranoid vein. While we "know" how the patient is behaving we are apt to be unaware how such knowledge is the product of an interaction involving a high degree of selectiveness and one's own "euphoric" or "paranoid" feelings and expectations of what will happen.

A delusion is usually defined as a distortion of reality arising from a disturbance of cognition or through the release of previously hidden or

repressed feelings. Yet all language is in some degree a distortion of reality. From a linguistic standpoint a delusion might be defined as a symbolic pattern which serves as a metaphorical representation of a person's problems and relationships. In a claim that "someone is poisoning my food" he is conceptualizing a series of traumatic interpersonal relationships in language which imparts to his statement a particularly vivid *feeling* of reality. In societies where the preparing and consuming of food form important channels of social relatedness and expressions having to do with tasting, regurgitating, digesting and defecating are significant ways of structuring experience, it is not surprising that metaphors concerning food should make experience vivid and valid. The feeling of truth arises more from the place of the symbolic element in a pattern of relatedness and the relation of the individual in his social environment than through any more "logical" thought process. Paradoxically, the delusional patient is not trying to escape reality but to experience it. While in one sense his behavior is bizarre, in another it involves the use of highly conventional stereotypes.

Language and Stress

Language serves both as an indicator of stress and as a mode of adaptation or defense. While the various somatic therapies differ in many ways, they have in common the subjection of the organism to stress and the production of alterations in brain function. In situations of extreme stress, the organism loses the capacity for complex interaction in the environment. Symbolism becomes more experiential, patterns are more highly condensed and stereotyped and the number of channels of interaction in the environment is reduced. The interplay among the levels of interaction is diminished so that symbolic elements become fixed in single patterns and the person becomes less aware of the interaction in the environment.

We have been interested in the manifestations of denial of illness (Weinstein and Kahn, 1950; Weinstein and Kahn, 1955; Weinstein et al. 1954). While most of the observations concern patients with brain injury, the principles of symbolic organization apply to behavior in other situations as well. The constellation of stress includes not only the brain lesion but the physical environment of the illness including the incapacity and the situation in which the behavior is being observed. The brain pathology not only acts as a stress but provides the milieu in which the adaptation occurs. This approach is particularly relevant to psychopharmacology because it conceptualizes relationships among symbolic, neural, motivational and social factors.

In the neurological literature denial of illness is designated as anosognosia, literally lack of knowledge of disease. It appears in the form

of denying such disabilities as blindness, hemiplegia, loss of a limb or eye, deafness, involuntary movements, manifest pain, etc. Patients also deny that they are ill in any way, that they are concerned about illness, the fact of an operation such as a craniotomy and personal and family problems. Denial of major disabilities appeared in enduring fashion with lesions which by reason of rapid development, central position, diffuseness or multiplicity, or association with increased intracranial pressure or sub-arachnoid bleeding were associated with a generalized usually bilateral slow-wave EEG rhythm. The syndrome did not occur with lesions confined to the cerebral cortex and cortical localization was more significant in determining which disability was to be denied than in the denial mechanism itself. The requisite neural milieu was also provided by bilateral prefrontal lobotomy. Anosognosia has also been reported in cases of barbiturate intoxication (WIKLER and RASOR) where patients attribute ataxic gait and dysarthric speech to untied shoe laces and missing teeth. Most interpretations of anosognosia view the phenomenon as a fixed defect due to a disruption of "body scheme" represented in a specific brain area or pathway, or as a manifestation of loss of insight. The inadequacies of these theories have been discussed in detail (WEINSTEIN and KAHN, 1955) and the present account refers only to those aspects that are relevant to concepts of symbolic behavior. It is important to note that the brain lesion does not "cause" the denial. Rather the milieu of brain function is the major factor in determining the language in which it is expressed.

Denial may be expressed in many forms other than in the specific negation of illness. It may be expressed verbally and nonverbally and not only in terms of the somatic environment but in concepts of place, time, person and event. Thus when asked about his illness a patient may laugh and joke. Or he may selectively withdraw by closing his eyes and remaining mute to questions about his incapacity (WEINSTEIN et al. 1955). Some patients with hemiparesis ignore that side of the body and the homonymous half of space and in drawing a picture of a human figure distort or omit the limbs on the side of the figure mirroring their own disabled limbs. In disorientation for place the patient misnames or mislocates the hospital while in disorientation for time he gives a date ante-dating the onset of his illness (PATERSON and ZANGWILL 1944), (WEINSTEIN and KAHN, 1951). Patients when shown objects of comparable complexity and familiarity characteristically misname only those which have to do with their problems, especially those of illness. They commonly misidentify other ill patients and doctors as old acquaintances and confabulate stories of activities obviously incompatible with illness. It is likely that anosognosia, disorientation, paraphasia and confabulation do not represent basically different neuro-physiological

mechanisms but are so categorized because of the space-time-matter idiom of our language.

While such denial is an enduring phenomenon and under the particular conditions of study can be correlated with alterations in brain function, the patient in many ways shows awareness of his disabilities. It was this troubling observation that led initially to formulations in terms of symbolic behavior rather than in the traditional psycho-physiological concepts. While a patient may admit that he cannot move his arm, he still may deny that it is paralyzed. He admits the fact of illness in one form of language but not another. In some cases, the patients with a paralyzed left limb says it belongs to someone else as a doctor or a nurse, or states that he has two left limbs (WEINSTEIN et al. 1954b). The very fact that he selects only a disabled member of the body to disown or duplicate indicates a degree of awareness. While a patient may misname an object he can generally demonstrate its use correctly. Though he may deny that there is anything the matter with him, he accepts hospital routine, taking medication and even submitting to operations without question. Also a patient may deny his disability to a doctor or nurse, but admit it to his relatives. Note was also made of the denial shown by the interviewer himself and denial and variations in the examiner's own attitudes may cause changes in the degree of denial expressed by patients (JAFFE and SLOTE). Patients who appear rather bland and distant often become animated in the course of expressing the denial, and actually the denial does not appear unless the patient is asked about his illness. It was for these reasons that the various phenomena of denial are considered to be what RIOCH has termed an artefact of a dyadic group.

To a great degree, the type of denial could be predicted by a knowledge of the content of symbolic adaptation that had been used prior to the onset of the illness. Thus patients who developed explicit verbal denial were reported by relatives as having previously denied illness, seeming to regard it as a form of weakness or failure. The maintenance of health was regarded as a personal responsibility tied up with self-esteem. Patients were apt to put off going to doctors and excuse or rationalize the manifestations of sickness. They were described as conscientious, compulsive, responsible people, and these attitudes were especially exemplified in attitudes toward work. For such people, health and work were ethical values. Through social relationships involving health and work, they gained a sense of "being". When ill or unable to work they were isolated and, through lack of a relatedness, did not derive such a feeling of self. Thus the manifestations of illness are not felt as "real" or as a part of one's own experience when they are not elements of a pattern of social relatedness. Patients with other forms of denial, such as with-

drawal and inattention and euphoria, were found to have utilized other symbolic themes in their pre-morbid existence.

The question arose of equating denial with a psycho-biological drive like the need or wish to be well. This is a useful concept but it has limitations, particularly in a heuristic sense. For example, it might imply that patients who show little or no denial do not want to be well to the extent that others do. It does not explain why the patient expresses his motives in words and gestures, rather than keeping them to himself, nor does it account for the divergence between the verbal behavior and his other activities. It does not take into account the adaptive significance of the highly banal, cliché-ridden speech of such patients. Finally, it does not lead to the understanding of why some verbal productions, which though they may not be ostensibly manifestations of denial, still function as modes of adaptation to stress. These involve the content as well as the structure of language and include confabulations, other forms of "social language" and changes in grammatical mood, tense and person.

Confabulation may be defined as the narration of a false version of an event or series of events that have putatively occurred in the past. In the literature, confabulation, exemplified par excellence in the Korsakow psychosis has been variously attributed to loss of memory, defective time sense and loss of ability to associate. Possibly because of the way a grammatical mode, i.e. past tense, predisposes to a particular type of selective interpretation, it has been considered that the patient is talking about the *past* and it has not been recognized that many confabulations are a metaphorical representation of *current* problems (WEINSTEIN et al. 1956). Thus a patient with intellectual deficits following a head injury may invent a story that he has been involved in a "counter-intelligence mission" whereas in fact he was hurt in an automobile accident. Another man with a head injury told a story of having been injured while "fixing the roof". When stressful incidents occur in the hospital situation they may pass with little comment by the patient only to appear in some changed version of the confabulation. It is for this reason that some confabulations appear so rambling and contain so many apparently irrelevant details. It is important to point out that talking about "counter-intelligence" or "fixing the roof" does not indicate hitherto repressed desires to be a CIC agent or a roofer, but they are metaphors describing the present situation.

Most confabulations of patients with head injuries involve rather stereotyped and popular themes. In others, the choice of symbolic content identifies the patient in a particular cultural role. In a military hospital, paratroopers who have sustained head injuries in automobile accidents frequently confabulate that they have been hurt while jump-

ing. In telling how the "parachute got fouled up" or how it "had a hole in the top" they not only represent their problem but use language which affirms identity and imparts "social reality" to experience. In this way the patient avoids isolation and anomie.

During the period when disorientation, confabulation and the various forms of denial are present, patients have little or no clinical anxiety. Considerably more evidence of anxiety is observed when these phenomena are sparse or transient. In the course of recovery, these symbolic patterns are succeeded by other forms of adaptive language which also seem to enable the patient to avoid anxiety (WEINSTEIN 1958). Even after a patient gives an accurate version of his illness and is completely oriented he may continue to offer the content of the confabulation in a new pattern. He may tell the identical story as if it had happened to someone else. Or he may preface the account with "they say" or "I used to think" or tell it as a rumor. Sometimes patients first talk of their own incapacities by describing similar ones in others. Or in answer to a query about their injury they may describe at length what happened to the car or to someone else. It is important to recognize that the "third person" is a figure of speech in which the patient is talking about himself. When he says that someone else was hurt in an accident he is not expressing "hostility" but symbolizing his own situation. Similarly, GOTTSCHALK and KAPLAN using a technic where patients with psychological conflicts were asked to speak about dramatic or personal life experiences, found that verbal references to other persons involving relevant content were important indicators of the subjective experiences of the patient. Patients in the course of recovery from brain injuries may also use the "second person". In response to the question "how do you feel" they may inquire "how do *you* feel ?" In addition to changes in grammatical tense and person, alterations in syntactical number may occur. For example, a patient may give an accurate account of his accident except that he will say that three cars were wrecked instead of two. Many languages have redundancies in their grammar and one factor in their persistence may be their uses in adaptation to stress. SULLIVAN has commented that use of the third person plural rather than the first person singular seems to facilitate communication of anxiety laden material.

Amnesia is not ordinarily thought of in terms of symbolic organization but is more often regarded as an "organic" memory defect or as a manifestation of "repression". Yet a study of a number of cases associated with head injuries and convulsive states (WEINSTEIN, 1957, 1959) indicates that amnesia has symbolic aspects in which the patient represents his problems and relates himself in his environment. When a patient says that he does not remember his accident or his operation

or coming to the hospital, he may be talking about his accident or its implications. When amnesias are selective the patients uses symbols that have been important in establishing social relatedness and personal identity. Thus a high school football star, incapacitated by an accident, could not remember having gone to school or playing football though he "knew" that he had. Similarly the last thing that a patient says that he remembers prior to the period of amnesia, whether true or fictitious, may symbolize current problems. As new traumatic situations arise they may be reflected in a change in the "last memory" generally in the temporal direction of the present.

Long after the patient who has been amnesic admits the facts of his accident he is apt to preface any statement about it with "I don't know" or "I don't remember but they say that ..." No patient who has had a severe head injury with loss of consciousness remembers the actual impact but if he is socially related he responds when asked with a statement of the accident. The patient who says "I don't know" seems to be expressing some feeling of non-involvement in the present situation and the "I don't know" and other negative expressions serve in the office of the amnesia.

Just as the "I don't remember" takes the place of the amnesia, so the various confabulations, disorientations, delusions and misidentifications may, as mentioned, be succeeded by forms of "social language" which also serve purposes of adaptation. Thus patients use many clichés and banalities in answer to questions that formerly elicited confabulations, etc. The head injury may be referred to in paraphasic fashion as a "hole in the head". The "third person" may appear in a threat (to a man with a similar incapacity) to 'beat his brains in'. This may be a patient's first reference to "brains". Cultural values such as "God", "home" and "Mother" may appear in such language patterns as vows and resolutions. Here a reference to God in profanity may have as much adaptive significance as if it were made reverently.

During the period when disorientation and confabulation are marked the patient generally expresses himself in a matter of fact way without much affect. Actually the most emotion is shown by patients with little or no disorientation. When a disoriented patient says that the hospital is across the street from his home he doesn't seem to say it with joy, regret or surprise. After brain function has improved, then he is apt to talk about going home in a highly emotional way. If he is then told that he may go he often decides that he really doesn't want to go, or he may persist in talking about going "home" even after being granted permission. Similarly, "third person" forms of language such as the vows and threats may be uttered with considerable emotion. It is not that the patient simply wants to go home and is "ambivalent" about it. Rather

"home" is an experiential symbol comparable to that used in disorientation for place. Nor is the emotion shown in a vow or threat simply an amplification of the verbal content, but there is a more complex relationship in which the expression of emotion itself may change the milieu of brain function so that a new level of interaction in the environment allows "home" and "mother" to operate in the experiential symbolic mode. A patient with a brain injury does not lack the capacity for affect so much as that he feels no need to use it. This concept may be germane to the observation that patients with delusions may appear indifferent to them while under the influence of drugs and become agitated when drugs are withdrawn.

Language as an Index of Behavioral Change

While language may serve as an index of therapeutic change as evidenced by the alterations paralleling variations in brain function, it is important to recognize that "therapeutic change" is only one aspect of behavior. Like many of the manifestations of a mental illness itself, the criteria of improvement are essentially social units. When a patient improves after taking a drug or after a somatic therapy, it does not necessarily mean that some metabolic error has been repaired or some undesirable component like anxiety or pain subtracted from the total behavior. Rather there is a reorganization of behavior in which symbolic elements appear in new patterns and the estimate of improvement may be largely a matter of the type, extent and duration of the adaptive processes. The greater the stress the more marked the adaptation may be and in this sense it may not be surprising that the more severe mental illnesses may derive more benefit from the somatic therapies than milder ones. These points may be exemplified by a discussion of the effects of pre-frontal lobotomy, ECT and barbiturates.

The procedure of bilateral lobotomy provides the milieu in which an enduring syndrome of anosognosia may exist. The success or failure of the operation seems to be a matter of the type and extent of denial that is used by the patient, his family and his doctor. If the patient explicitly denies his problems or when he expresses lack of concern over them with a smile, then the result is a "successful" one. The fact that he denies the operation too may not be regarded as significant. When the adaptation is one of extreme withdrawal with neglect of the person or is one of manic or sexy behavior, then the procedure is considered as not having been of benefit. The apathy or silliness are not simply undesirable complications of the operation to be remedied by deeper or more medial or lateral cuts, but forms of adaptation that are not culturally acceptable whereas expressions of explicit denial are eminently acceptable.

KAHN and FINK (1954) studied the changes in language that occurred in the course of ECT and correlated them with independent evaluations of clinical improvement. They found that patients rated as improved showed many more alterations in language pattern than did those graded as unimproved. Prior to treatment patients generally referred to the illness and expressed their problems in the first person and the present tense. During shock treatment, the improved group made much more use of the past and future tense and second and third person. They made more statements of denial and negation, utilized more qualification of terms and employed more stereotyped and cryptic expressions and clichés. In a total of 65 patients, 68% in the improved group showed three or more of such language categories contrasted with 20% of the unimproved group. The authors believe that the degree to which patients' families are made more comfortable by the changed language and use similar language themselves is a determining factor in the duration of improvement following treatment.

Similarly when ECT was used in cases of intractable pain (WEINSTEIN et al. 1959) it was shown that only improved cases expressed the denial of present and past pain and associated disabilities and showed disorientation. They also described their pain in metaphorical terms, used the "third person" and showed euphoric and paranoid behavior.

The effect of barbiturates on symbolic behavior was studied both in patients with brain injuries and in those with physical disabilities unassociated with brain pathology. When barbiturates are administered to patients who are disoriented and express denial there is usually little change in symbolic behavior. If the drug is administered intravenously to patients with brain disease who show no clinical alterations in behavior or who have recovered from a state when such changes were present, a large proportion (68% of 600 patients tested to date) show denial and disorientation. This observation forms the basis for the "amytal test" for brain disease (WEINSTEIN et al. 1953, 1954c). In this technic the patient is given a standard list of questions pertaining to his disability, orientation and the identification of the examiner. After enough drug (usually from 0.35 to 0.45 gms.) has been given to produce errors in counting, nystagmus and slight drowsiness, the questions are repeated and persisting errors in orientation and enduring denial of the major disability are regarded as a positive result, i.e., evidence of the existence of structural brain injury. The following is abstracted from a "positive amytal" in a patient with an infiltrating brain tumor tested in St. Thomas in the Virgin Islands. He had been admitted to the Knud Hansen Memorial Hospital because of headaches and a convulsive seizure.

Pre-amytal.

(What is your main trouble) My head.
(Why did you come here) Because I had this thing happen to me. I fell to the ground.
(What is the name of this place) Hospital.
(What is the name) Hansen Memorial Hospital, Knud Hansen Memorial Hospital.
(What did you do last night) I slept.

After injection of 0.3 gms. of amobarbital sodium

(What is your main trouble) Trouble.
(What is your main trouble) I don't know.
(Why did you come here) I don't know, maybe someone else can tell.
(What is your main trouble) Do you know what it is?
(What is the name of this place) It's an office, I suppose.
(What is the name of this place) I don't know.
(What did you do last night) I was at a hotel.

The interview illustrates, in addition, the use of the "I don't know" and "second and third person" mechanisms.

KAHN et al. noted that the incidence of positive amytal tests can be correlated with clinical improvement during ECT. In a group of 24 cases (14 depressions, 9 schizophrenic, 1 manic) patients rated as "much improved" showed 100% positive amytal tests after 7—9 treatments, those considered "moderately improved" had 60% positive reactions after 7—9 treatments, while the "unimproved" group had only 25% positive tests after 10—12 treatments. In the 10 patients receiving ECT for intractable pain, positive amytal tests were obtained in each of the 4 "improved" patients, in one of the 4 moderately improved cases and in neither of the unimproved even after 14 treatments (WEINSTEIN et al. 1959).

In patients whose ailments do not involve the central nervous system, the amytal test is negative; that is patients do not persistently deny illness explicitly or become disoriented. The majority of patients, however, show certain changes in language that are important as adaptive mechanisms (WEINSTEIN and MALITZ, 1954). These are the use of the third person, changes to the past tense, the increased use of metaphor, colloquialisms, slang, humor and profanity, more "concretization" of symbols and more experiential and personalized naming. Thus prior to the drug injection a patient may state that he came to the hospital because "I have diabetes". When the question is repeated after the administration of the drug, he may respond with "they said it was diabetes" or "it was diabetes". Questions about his own illness, which prior to the drug injection were answered in the first person and present tense, now may be answered by the patient with an account of the ailments of his relatives. More "concrete" and "paraphasic" sym-

bols are exemplified by the patient referring to the interviewer in such terms as "needle sticker" and to a skull depression as a "saucer". There is more use of qualifying statements such as referring to the examiner as Dr. X, *my friend*, and to the hospital as WALTER REED, *the very best*. Clichés and colloquialisms occur more frequently and these may become highly condensed as in the case of a woman who telling of her difficulties at home stated that "everyone has an axe to be hoed". When asked about their "main trouble" some patients reply with such comments as "I'm not in trouble" or "Just wife trouble". All of these language changes reflect a shift from a referential to the experiential mode of symbolic patterning. Thus while "Dr. X" is a referential symbol, "Dr. X, my friend" is much more of an experiential one. When such altered language patterns can be elicited under amobarbital sodium prior to ECT, the likelihood of a successful therapeutic outcome is significantly greater (KAHN and FINK, 1954).

Mood changes, classed as euphoric or paranoid appeared in most patients with or without pre-existing brain injury under the conditions of barbiturate administration that have been described. As has been mentioned, the labelling of "euphoric" and "paranoid" involves an interpersonal transaction including the observer's own feelings. While euphoric and paranoid behavior tend to be opposites in terms of "emotion", from the standpoint of language pattern they are similar. In each there occur selective misnaming and misinterpretation, a shift to more "concrete" and experiential symbols and the use of the "second" and "third person". Thus the same drug, barbiturates, may cause either drowsiness and withdrawal, euphoric or paranoid behavior in different or even the same persons. While these may be "different" actions in one sense, they all involve an adaptive process with a change from a mainly referentially communicative system to a predominantly experiential symbolic mode. The non-verbal components of mood, the gestures, tone of voice, etc. may be regarded as helping to determine the place of the verbal element in the referential-experiential scale.

These observations cast doubt on the traditional explanation of the therapeutic effects of barbiturates and other drugs as advanced in the concepts of "abreaction" and the "release of repressed material". WIKLER has criticized the circular reasoning which assumes the validity of these concepts. There is evidence, further, that some of the "released" material may be confabulatory (GERSON and VICTOROFF), (REDLICH, RAVITZ and DESSION). Whether the patient's statements are true or false is not as important in that he is using the content in metaphorical fashion and past tense to depict current problems. The meaning derives as much from the interpersonal situation as from the verbal content itself. The matter of veracity also does not seem to have been of

importance to the investigators as the truth of the various stories does not seem to have been checked. The few interviews of which verbatim accounts have appeared in the literature have a highly melodramatic, ludic[1], stereotyped quality. One report (ADATTO, 1949) describes a narcoanalysis with a convicted wife-murderer. When asked about his mother, he replied "she is all right. She has lived a hard life. She has had a tough time (tears)". Here it is more likely that the patient is expressing feeling about himself and his predicament rather than telling of his mother in a referential sense. The therapeutic effect, if any, would seem to come not through "release" or "abreaction" but through the use of the symbolic element in an altered pattern of interaction.

Another method of recording language changes has been developed by JAFFE (1957, 1958). Using the type-token ratio (TTR) JAFFE investigated patterns of language as a function of a two person situation or dyad. The TTR is the number of different words used by both speakers divided by the total words used. Thus in a case of denial of illness where a dialogue might run as follows:

Question: What is wrong with you?
Answer: There is nothing wrong with me.
Question: Are you sure there is nothing wrong?

the TTR would be low. JAFFE finds that low TTR's (repetitive verbal transactions) occur in states such as anxiety which interrupt the flow of referential communication. With ECT (JAFFE, FINK and KAHN, 1960) there was a consistent decrease in the mean TTR and an increase in variability (standard deviation) about the mean. These findings correlated with changes in grammatical pattern (FINK, JAFFE, KAHN, 1959) so that with increased alteration in syntactical structure there is a decrease in language diversity with greater stereotypy and repetitiveness. Also changes in the TTR and in syntactical structure correlated with percentages of δ EEG activity. This method has the distinct advantage that it uses a spontaneous type of conversation rather than the rather artificially constrained structured interview. In all these procedures the index of stress and the measure of "anxiety" is also the measure of the adaptation.

On the basis of observations of the behavior of patients with brain injury, those receiving barbiturates and those undergoing ECT, a common hypothesis for therapeutic effect was evolved. It was considered that in each of these situations there was created a milieu of altered brain function in which new patterns of symbolic adaptation or interaction in the environment could be evolved and maintained. This

[1] Ludic is the term used by JEAN PIAGET to describe the play, initiative and dramatic aspects of behavior in young children. It provides a useful linking of comic and tragic manifestations in a single category.

hypothesis has been applied to the general study of drug actions by FINK et al. It was expected that drugs like amobarbital which produce more "synchronized" EEG activity would be associated with similar changes in language pattern and by a decrease in language diversity as measured by the TTR. Drugs like mescaline and LSD-25 which produce minimal changes in the resting EEG generally in the direction of "desynchronization" (WIKLER) should not be accompanied by such alterations in syntax and should be associated with greater variability in speech patterns. A study of the effects of chlorpromazine has supported this formulation. With diethazine, a drug causing irregular desynchronized EEG activity, syntactic patterns either did not change or did so in a direction opposite from that occurring with ECT and speech became more variable. Further, in patients who had received ECT, diethazine abolished the changes in language pattern that had appeared during the shock treatment.

There are, of course, many other ways of studying language and correlating it with the other aspects of behavior. This review has been confined to the development of a particular conceptual orientation and an account of methods that have actually been used in the observation of drug effects. For linguistic analyses to be of value in psychopharmacology, they should fulfill a number of criteria. They should have a significant degree of correlation with other behavioral categories. They should not be so detailed as to require a monumental recording and statistical operation, a disadvantage with some microlinguistic and phonemic analyses. Most important they should not only measure existing psychological and physiological categories but lead to new concepts that change our current ideas of what physiological and psychological functions are.

No article on psychopharmacology would be complete without some mention of the language of psychopharmacologists. While terms like "tranquilizing" and "energizing" are useful in describing the behavior of patients and their doctors, this does not mean that drugs "tranquilize" or "energize" the nervous system. Nor do drugs actually "bleach anxiety" or make delusions "fade away". Here one's thinking may fall victim to the classificatory suggestiveness and comforting implications of the terms themselves. A word to the wise may not be sufficient.

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Mepazine (Pacatal): Clinical Trial with Placebo Control and Psychological Study

By

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Introduction

Mepazine acetate, a phenothiazine derivate, was introduced for use in the United States in 1955 by Kline and Jacob.

In clinical literature through 1958 available for review 10 authors reported the drug was an effective tranquillizer (Bowes, Braun, Bruckman et al., Feldman, Flipse, Friedgood, Hiob and Hippius, Hutchinson, MacGregor, Sarwer-Foner and Koranyi). Denber and Kline reported it to be relatively ineffective. Side effects were reported mild in all studies, except those reported by Bruckman, Denber, Feldman and Kline, which reported moderate to marked dizziness, drowsiness, blurred vision or constipation. A synergistic action when mepazine was administered with other phenothiazines was noted by Bowes, Braun, Bruckman et al., and by Hiob and Hippius. Controls for medication effect, if employed, were intra-individual. No studies employed inter-group control.

In one of the earlier studies (Hutchinson) it was observed that patients reported their minds "much clearer", "able to plan and think much more easily" or "clear in the head". Subsequent studies repeated or suggested the substance of these reports. "It leaves the sensorium clear at all doses. The patient's capacity to think and to concentrate is retained when this was originally unimpaired" (Sarwer-Foner and Koranyi).

The American Medical Association Council on Drugs reported "It is said to exert a selective action to normalize the thinking process of mentally or emotionally disturbed patients" (Kautz). Agreement on such an effect was not uniform: "... this investigation does not confirm its ability to 'normalize the thinking process'" (Denber). However, no psychological testing was reported to confirm or to specify such psychological changes.

The present study was undertaken to determine whether addition of mepazine to the medication of patients already receiving a pheno-

thiazine would result in changes in (a) clinical status, (b) somatic symptoms, or (c) performance on psychological tests selected to describe aspects of intellection.

Material and Methods

Material. 60 patients were selected on a Continued Treatment Service to fit criteria: sex male; diagnosis schizophrenic reaction without re-

Table 1. *Selected clinical characteristics of the trial population*

Group	Age (years)					Mental Hospitalization Duration (months)			Psychiatric Diagnoses by Type of Schizophrenic Reaction				
	Distribution					Mean	Present Mean	Total Mean	Simple	Heb.	Cat.	Par.	Mixed or Undiff.
Mepazine	10—19	20—29	30—39	40—49	50—59	35.8	85.3	97.3	0	3	8	14	5
	0	8	11	9	2								
Placebo	1	6	7	13	2	39.3	109.5	126.2	1	1	10	13	5
	1	6	7	13	1								

Table 2. *Number of patients in each group by concurrent other medication, with dosages*

Medication	Chlorpromazine			Promazine		Prochlorperazine			Hydroxyzine		Methylphenidate		No other medication	
Patient Group*		M	P	M	P	M	P		M	P	M	P	M	P
Dosage (Total daily dosage in milligrams)	0—100	1	0	101—200	0 2	45	0	1[3]	101—150	1 0	20	1 0	2	2
	101—200	6	5											
	201—300	5	7[1]											
	301—400	2	3											
	401—500	0	1[2]											
	501—600	5[1]	7											
	1101—1200	1												
Totals		20	23	0	2	0	1		1	0	1	0	2	2

* M = Mepazine, P = Placebo.

Figures with superscript indicate one patient with additional daily medication as follows: [1] Reserpine 3mg., [2] Promazine 300 mg., [3] Chlorpromazine 25 mg.

cognized brain damage; age 20—60, hospitalization continuous for one year or more, and relatively stable psychiatric clinical status. The criterion of medication including a phenothiazine other than mepazine for at least six weeks prior to selection could not be attained for six in the total population, when the other criteria had been met (4 in drug, 2 in placebo group). Selected biographical and clinical characteristics of the population appear in Table 1. Final trial number was 24 for the mepazine group (drop-outs were — 3 escapees, 2 discharges, 1 transfer for unrelated medical complication) and 28 for the placebo group (drop-outs were — 1 escapee, 1 rating failure).

Methods. *Drug administration and placebo control.* Mepazine was provided as 100 mg tablets and placebo as tablets containing starch, methylcellulose, lactose, magnesium stearate, and water. Supplies were delivered to the ward physician labeled "Lissol 1" and "Lissol 2" together with two lists of 30 patients each. To reduce bias "mepazine" or "Pacatal" was never identified by name to any ward personnel. That the medication was mepazine was known only to three research personnel (DK, GL, and JW), and that "Lissol 1" was mepazine and "Lissol 2" was placebo was known only to trial coordinator, who did no experimental ratings.

The trial medications were represented as forms of a new medication which might result in patient improvement. The ward physician was instructed (a) to begin administration of 3 tablets daily without change in pre-trial medication unless required by side-effect or other medical change, (b) to use neostigmine 15 mg for side-effect as required, but only after report to coordinator, (c) to maintain fixed dosage at 3 tablets daily. Fixed rather than sliding dosage was selected to reduce variables and to facilitate administration in event mass-therapy was advisable; staff-patient ratios in large state hospitals often limit individualized dosage. Since usual daily dosage reported was 100—300 mg, with dosage range of 75—100 mg, total daily dose was set at 300 mg. Table 2 presents medication and dosage characteristics of the trial population. Trial period was January 12 to April 1, 1959 (9 weeks).

Observations

Observations were limited to pre-trial and end-of-trial periods, reducing trial process stimuli to the acts of medicating and to the somewhat increased attention of the ward personnel by their knowledge of the trial. Observations were made as follows:

1. Psychological Special. The research psychology group performed two types of examinations: A. Picture Arrangement, Block Design, Comprehension and Similarities subtests of the Wechsler Adult Intelli-

gence Scale[1], B. the Epstein Test of over-inclusive thinking[2]. The Wechsler Adult Intelligence Scale sub-tests used were chosen because of the greater probability of their scores changing (as compared to the vocabulary test, for example) if the patients changed. Since improved clarity of thinking was expected and lack of clarity of thinking would effect these sub-tests negatively, the sub-tests were deemed appropriate both in sensitivity and relevance. The Epstein Test had been found to be negatively affected by psychopathology, and requires clarity of thought. However, it involves a different intellectual task than any of the Wechsler Adult Intelligence Scale sub-tests.

2. Psychiatric Clinical. The research psychiatrist conducted mental status interviews, providing ratings of thought disorder as mild, moderate, or marked, and of clinical status on a 5 point scale as markedly improved, slightly improved, unchanged, worse, and markedly worse. The latter scale was subsequently simplified by condensation of the two "improved" and "worse" categories.

3. Nursing Clinical. The ward head nurse observed the study population with special care, and rated the members on the same scale used by the psychiatrist.

4. Attendant Clinical. The ward attendants were interviewed by the psychiatric social worker, who employed the multifactorial Hospital Adjustment Scale of FERGUSON et al., and recorded their responses.

5. Selected somatic symptom (side-effects) survey. A survey for incidence of selected somatic symptoms was conducted during the eighth week by research nursing personnel. A questionnaire was prepared listing 14 "side-effect" symptoms of mepazine, by supplement and modification of the listing prepared by FELDMAN. Although a pre-trial survey was not conducted, occurrence of specific symptoms not *usual* for the patient was reported by attendants who knew each patient best. An additional incidental overall estimate of change in clinical status was obtained from these ward personnel during the conduct of this survey.

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[1] The Wechsler Adult Intelligence Scale is published by the Psychological Corporation, 304 East 54th Street, New York City. In the Epstein Test, a series of 50 key words is given, each key word followed by five words including the word "none". The subject is asked to underline only those words that are absolutely necessary to make a complete thing that the key word described. For example, if the key word is "house", the words following it are wall, curtains, telephone, bricks, roof and none. Schizophrenic patients in the original study (EPSTEIN), and manic-depressive patients in a second study [PAYNE, R. W., and H. L. HIRST: Over-inclusive thinking in a depressive and a control group". J. Cons. Psychol. **21**, 186—188 (1957)] were found to "overinclude" significantly more than normals, that is, they tended to underline many words that were not "absolutely necessary".

[2] Published by Consulting Psychologists Press, Palo Alto, Calif.

The two ratings by psychiatrist, and the ratings by ward nurse and by attendants on side-effects survey were subsequently grouped as "impressional" reports, since they represented determinations based upon a summary of judgements by an observer rather than upon judgements of specific behavioral occurrences (in the case of the Hospital Adjustment Scale), or upon behavior during measurement of limited aspects of function (in the psychological testing).

6. Laboratory. Complete blood count and hematocrit was performed on all patients in the mepazine group on six occasions before and during the trial period.

Results

Psychological examination results and Hospital Adjustment Scale attendant ratings are provided in Table 3. The results of four im-

Table 3. *Results of psychological tests and HAS behavioral ratings*[1]

Test or rating	Placebo means			Mepazine means			t of the difference between placebo and mepazine	t necessary for significance at the 0.05 level of probability
	pre	post	difference	pre	post	difference	group differences	group differences
WAIS								
Comprehension . .	77.62	82.76	5.14	73.76	75.88	2.12	0.38	−2.05
Similarities	74.38	78.76	4.38	70.84	76.00	5.96	−0.24	−2.05
Block Design . . .	78.86	85.10	6.24	84.64	79.44	−5.20	0.17	−2.05
Picture Arrangement	70.45	71.14	0.69	63.76	71.12	7.36	−1.08	−2.05
Total WAIS Score .	77.21	81.79	4.59	75.72	78.28	2.56	0.52	−2.05
EPSTEIN								
Overinclusion . . .	52.66	50.76	−1.82	47.04	57.75	10.71	−1.14	2.06
Underinclusion. . .	20.52	21.90	1.38	24.25	21.67	−2.58	1.13	2.06
Total Incorrect . .	73.18	72.66	−0.52	71.29	79.42	8.13	−0.99	2.06
HAS								
Area I	64.79	64.24	−0.53	61.04	68.88	7.83	−1.20	−2.05
Area II	54.20	63.00	8.47	61.17	76.42	15.25	−0.85	−2.05
Area III	58.77	61.73	2.97	64.79	62.83	−1.96	0.12	−2.05
Total Score	59.93	62.73	2.80	62.13	70.04	7.50	−0.78	−2.05

[1] Average test scores of patients, and their changes from pre to post trial, in the mepazine and placebo groups. The obtained scores and the scores necessary for statistical significance are given. None of the test differences were significant (see text on Table 3 on separate sheet).

WAIS and HAS: Positive increases (pre- to post-differences) mean improved performance. However, a negative t test is in the direction of greater improvement for the mepazine group.

EPSTEIN: Negative increases (pre- to post-differences) mean improved performance. However, a positive t test is in the direction of greater improvement for he mepazine group.

Table 4. *Impressional ratings*

Group	Improved		Worse		Unchanged	
	M	P	M	P	M	P
1. Psychiatrist: Clinical status	10	7	2	3	12	18
2. Psychiatrist: Thought disorder. . . .	6	2	2	2	16	24
3. Head Nurse: Clinical status	9	9	2	6	13	13
4. Side-effects Survey: Clinical status . .	6	3	0	3	18	22

M = Mepazine, P = Placebo.

Table 5. *Selected somatic symptom survey*

Number of patients with one or more symptoms		Specific symptom incidence								
		drowsiness	mouth dryness	headache	blurred vision	g. complaint	dizziness	depression	slurred speech	total
Mepazine	6	4	3	3						10
Placebo	12	7	5	4	3	3	2	2	2	29

pressional ratings are presented in Table 4. Selected-symptom survey data is presented in Table 5.

There were no marked or sustained changes in the serial laboratory observations.

Discussion

The two groups were not significantly different in any dimension by the Wechsler Adult Intelligence Scale, Epstein Test or Hospital Adjustment Scale scaling (Table 3). In both groups the trend was toward improvement in most parts of the Wechsler Adult Intelligence Scale and in the Hospital Adjustment Scale. On the Epstein test there were changes in both directions. The placebo group performance was somewhat better on the over-inclusion score, the most sensitive part of the Epstein Test, but the difference was not statistically significant[1]. The usual expectation with most test-re-test data is for improvement in any group by practice effect. In a group receiving an effective drug, change in an observed function or aspect should be greater than in a group receiving placebo, to a statistically significant degree. This was not the case for these three measures employed, indicating that the use

[1] The examining psychologists became aware that some of the patients had difficulty reading the words of the Epstein Test during the end-of-trial testing. The majority of these patients were in the medication group. The examining psychiatrist also noted visual deficit during his interviews, but this was not noted for the mepazine group by attendants during the somatic symptom survey (see Table 5).

The statistical method employed was the Fischer-Yates simplification of FISCHER's Exact Probabilities Test, in Sidney Siegel, "Nonparametric Statistics", by Sidney Siegel. New York: McGraw-Hill 1956.

of mepazine in conjunction with other phenothiazine drugs does not have the effect of improving the thinking of schizophrenic patients or improving their hospital behavior.

Although the majority of subjects in both groups remained unchanged on the four "impressional" ratings, there were more patients in the drug group than in the placebo group who improved. A statistical test was made, using only the changed subjects, to determine whether the direction of the change was of sufficient size to be considered beyond chance variation. When each of the ratings was tested, none of them indicated difference beyond chance expectation.

A surprising result of the selected somatic symptoms ("side-effects") survey (Table 5) suggested that more patients in the placebo group showed side-effects, with more recorded symptoms, than did patients in the medication group. Some systematic error in conduct of this study could not be disclosed by review of the symptom-frequency reports by the several observers, or of observer-patient loads. That the difference was not due to overloading of placebo group by patients receiving phenothiazines is shown in Table 2, where daily dose-range frequencies are comparable. This observation was so unexpected that an experiment was conducted on 2 groups of 6 albino rats. The observation that death, preceded by convulsions, occurred only in the group receiving intraperitoneal suspension of Lissol 1 confirmed that these tablets contained mepazine. It is probable that an atropine-like property of mepazine decreased the incidence of these selected symptoms accompanying medication with other phenothiazines. Although the differences in somatic symptom frequency between medication and placebo groups were not significant by the chi-square test, decrease in such symptoms during mepazine therapy has been observed before (Bowes, Bruckman et al., and Hiob and Hippius), and suggests some clinical value for the combination of mepazine with other phenothiazines.

Summary

A placebo-controlled double blind study is reported of a nine-week trial of mepazine in fixed daily dosage of 300 mg on a hospitalized population of 60 male chronic schizophrenic patients, the majority already receiving another phenothiazine.

There was no statistically significant difference between drug and placebo group for any of 8 measures employed, including two psychological tests selected to describe aspects of intellection. On four impressional measures there were more patients in the drug group than in the placebo group who improved, or who evidenced less somatic symptoms; however, statistical treatment of the data describing these differences showed no variation beyond chance.

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J. R. Crawford, M.A., Psychiatric Social Worker, conducted the Hospital Adjustment Scale interviews. Medication administration was a joint responsibility of E. Alesi, R.N., and W. Byank, R.N., Supervising Nurses of institute and hospital respectively. M. Seaman provided stenographic assistance.

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The Effect of Perphenazine on the ACTH Release Induced by Neurotropic Stress*

By

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Tranquilizing drugs such as chlorpromazine, reserpine and related compounds are of value in the treatment of various types of emotional disturbances in man. In experimental animals, too, they have been found to prevent in a great measure the effects induced by stress, *e.g.* by inhibiting the strong ACTH release [*e.g.*, Hamburger (1955), Olling and DeWied (1956), Sevy et al. (1957), Mahfouz and Ezz (1958), Mäkelä et al. (1959)].

Recently a new derivative belonging to the chlorphenothiazine group, perphenazine, has been developed, of which group also chlorpromazine is a member. The purpose of the present work was to determine the effect of perphenazine on the ACTH release induced by neurotropic stress. The adrenal ascorbic acid depletion was used as an indicator of ACTH release [Sayers (1950)].

Material and methods

Altogether 147 white male rats weighing about 200 g each were used for experimental animals. They were divided into the following groups of seven animals each:

Acute experiments. 1a. Intact controls. These rats were killed immediately after being taken from the cage and had received no treatment.

1b. Controls to which a subcutaneous injection of 0.2 ml physiological sodium chloride solution was administered $1^1/_2$ hours prior to killing.

2. The animals in this group were injected subcutaneously with perphenazine [1-(2-hydroxyethyl)-4-(3-(2-chloro-10-phenothiazyl)-propyl)-piperazine,] "Trilafon" in a dosage of 0,5 mg per 100 g body $1^1/_2$ hours before killing.

3a. The rats of the neurotropic stress group were kept for one hour each in its own small cage, where they were irritated by means of strong sound and light stimuli.

3b. The animals of the perphenazine + neurotropic stress group were subjected simultaneously, during one hour, to the stimuli described

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above but they were injected, $^1/_2$ hours prior to this, with perphenazine in a dosage of 0.05 mg per 100 g body weight.

4a. The animals were treated as in Group 3a.

4b. The animals were treated as in Group 3b except that the perphenazine dosage was 0.1 mg per 100 g body weight.

5a. The animals were treated as in Group 3a.

5b. The animals were treated as in Group 3b except that the perphenazine dosage was 0.25 mg per 100 g body weight.

6a. The animals were treated as in Group 3a.

6b. The animals were treated as in Group 3b except that the perphenazine dosage was 0.5 mg per 100 g body weight.

7a. The animals in this group were injected subcutaneously with 5 I.U. ACTH per 100 g body weight and killed after $1^1/_2$ hours.

7b. The animals were injected with ACTH like those in the preceding group; additionally they were injected with perphenazine half an hour prior to this, in dosage of 0.5 mg per 100 g body weight.

8a. The animals were injected subcutaneously with pitressin in a dosage of 1 I.U. per 100 g body weight and killed after $1^1/_2$ hours.

8b. The animals in this group were injected with pitressin like those in the preceding group; additionally they were injected with perphenazine half an hour prior to this, in a dosage of 0.5 mg per 100 g body weight.

Chronic experiments. The test animals were injected subcutaneously with 0.5 mg perphenazine per 100 g body weight daily. On the third, fifth and 9th day of treatment, half an hour after the perphenazine administration, seven animals in each instance were subjected to neurotropic stress during one hour in the same manner as the rats of the acute test groups (Groups 3 to 6) and killed thereafter. On each one of the above-mentioned days a corresponding number of rats were also simultaneously subjected to the same kind of neurotropic stress during one hour without any preceding treatment and subsequently killed.

All the animals were killed by rapid decapitation. The adrenals were immediately removed from the surrounding tissue and weighed on the torsion balance. They were then homogenized in 4% trichloracetic acid and their ascorbic acid content was determined according to SCHAFFERT and KINGSLEY (1955).

Statistical treatment. The *t*-test was employed in the statistical treatment of the results. The difference between the means was considered to be statistically significant when the value of P was $\leqq 0.05$.

Results

It can be seen from Table 1 that injection of mere physiological sodium chloride solution induced adrenal ascorbic acid depletion, but

Table 1. *Adrenal ascorbic acid concentration (mg/100 g fresh tissue) in control and test animals in acute experimentals*

Group	Treatment	Dosage of the drug mg/100 g body weight	Number of animals	Adrenal ascorbic acid mg/100 g fresh tissue	p^{**}	p^{***}
1a	Intact controls		7	415 ± 9.1*		
1b	Controls treated with 0.9% NaCl		7	387 ± 15.0	> 0.05	
2	Perphenazine		7	311 ± 11.3		< 0.001
3a	Neurotropic stress		7	267 ± 4.6		< 0.001
3b	Perphenazine + Neurotropic stress	0.05	7	260 ± 4.2	> 0.05	< 0.001
4a	Neurotropic stress		7	270 ± 10.6		< 0.001
4b	Perphenazine + Neurotropic stress	0.1	7	279 ± 6.4	> 0.05	< 0.001
5a	Neurotropic stress		7	264 ± 10.2		< 0.001
5b	Perphenazine + Neurotropic stress	0.25	7	284 ± 12.6	> 0.05	< 0.001
6a	Neurotropic stress		7	248 ± 14.7		< 0.001
6b	Perphenazine + Neurotropic stress	0.5	7	325 ± 8.9	< 0.001	< 0.001
7a	ACTH		7	233 ± 9.8		< 0.001
7b	Perphenazine + ACTH		7	240 ± 13.2	> 0.05	< 0.001
8a	Pitressin		7	290 ± 7.2		< 0.001
8b	Perphenazine + Pitressin		7	282 ± 8.7	> 0.05	< 0.001

* Standard error.
** P compared with group a.
*** P compared with intact controls.

the difference as compared with the intact controls was not statistically significant. Administration of perphenazine, too, caused adrenal ascorbic acid depletion, the difference as compared with intact controls as well as those controls injected with physiological sodium chloride solution being highly significant. The same table reveals further that the neurotropic stress applied in this work produced a highly significant ascorbic acid depletion, as compared with the controls.

When perphenazine was administered $^1/_2$ hours prior application of stress, the subcutaneously injected dose of 0.5 mg per 100 g body weight, which was still well tolerated, was able to inhibit in a highly significant degree the adrenal ascorbic acid depletion induced by neurotropic stress. The lower dosages employed in this work did not have such an effect. However, the 0.5 mg perphenazine dosage per 100 g body weight could not entirely prevent the decrease of ascorbic acid content in the adrenals due to neurotropic stress, the difference as compared with the intact controls being highly significant, and as compared with the controls injected with physiological sodium chloride very significant. On the other hand perphenazine was not able to prevent the adrenal ascorbic acid depletion produced by ACTH or by pitressin.

Table 2. *The response of adrenal ascorbic acid to neurotropic stress after 1—9 days perphenazine treatment*

Treatment days	Stress group		Perphenazine + stress group		% Difference	P**
	Number of animals	Adrenal ascorbic acid mg/100 g	Number of animals	Adrenal ascorbic acid mg/100 g		
1	7	248 ± 12.6*	7	325 ± 8.9	+33	< 0.001
3	7	255 ± 9.2	7	329 ± 10.1	+29	< 0.001
5	7	262 ± 12.8	7	329 ± 8.0	+26	< 0.01
9	7	270 ± 7.8	7	262 ± 16.2	− 3	> 0.05

* Standard error.

** P indicates the probability of the difference between stress and perphenazine + stress groups.

It can be seen from Table 2 that as late as on the fifth day of daily treatment by perphenazine injections this drug was able to inhibit in a very significant degree the adrenal ascorbic acid depletion induced by neurotropic stress, while it did not have such effect any more on the ninth day.

Discussion

The results obtained in this work show that like chlorpromazine (another member of the chlorphenothiazine group) perphenazine is able under acute experimental conditions to inhibit the ACTH release induced by stress, at least as regards the neurotropic stimuli applied in the present work. This is in agreement with observations, by which in experimental animals in general tranquilizing drugs have been found to inhibit the ACTH release produced by stress [*e.g.* HAMBURGER (1955), OLLING and DE WIED (1956), SEVY et al. (1957), MAHFOUZ and EZZ (1958), MÄKELÄ et al. (1959)]. However, when perphenazine was given continuously once a day, it was no longer able on the ninth day of such treatment to prevent the ACTH release. At that time, then, adaptation has occurred in this respect, which is also in agreement with earlier observations relating to tranquilizing drugs [*e.g.* GUILLEMIN (1956), MÄKELÄ et al. (1959)].

From the results the inference can be drawn that perphenazine does not block the adrenal ascorbic acid depletion, which was used as an indicator of ACTH release, by any mechanism immediately affecting the adrenal cortex since it was not able to prevent the adrenal ascorbic acid depletion induced by exogenous ACTH. On the other hand, it is a generally known fact that pitressin contains the hypothalamic neurohumoral substances causing ACTH release from the adenohypophysis [*e.g.* SAFFRAN et al. (1958), GUILLEMIN (1958)]. Since the drug could not prevent the ACTH release produced by pitressin, the inhibition obviously does not take place at the level of the adenohypophysis. The

inhibitory effect of perphenazine upon stress-induced ACTH release is therefore based on its effect upon the central nervous system, which is indeed the principal point of effect of tranquilizing drugs of this kind.

Recent neuroendocrinologic research has shown that the hypothalamus plays a highly central role in the regulation of the activity of the adenohypophysis, particularly as regards neurotropic stimuli [HARRIS, (1955)]. Since, according to several investigations, chlorphenothiazine derivatives depress the hypothalamus and the formatio reticularis [COURVOISIER et al. (1953), HIMWICH and RINALDI (1957)], it is conceivable that the inhibitory effect of perphenazine upon stress-induced ACTH release would be based on this circumstance. Also it is know that the formatio reticularis plays a central part in the transmission of neurotropic stimuli to the hypothalamus [*e.g.* MAGOUN (1958), SMELIK (1959)] and since it has been established that perphenazine primarily affects the formatio reticularis [*e.g.* KODAHL (1958)], it would seem logical that the inhibitory effect upon the stress-induced ACTH release too, would occur just there. Again, perphenazine itself had an ACTH release-inducing effect, obviously owing to a nonspecific adrenocorticotropic stimulus, which is generally caused by treatment with any pharmacological substance [*e.g.* GUILLEMIN (1956)], this affect acting either directly upon the adenohypophysis or by way of the hypothalamus [FORTIER (1951), HARRIS (1955)]. This probably also furnishes an explanation of the fact that an adrenal ascorbic acid depletion occurred in the perphenazine + stress group, which was equal to that in the animals merely administered with perphenazine. In this case, obviously, the strong ACTH release induced by stress cannot take place owing to blocking of the stimuli primarily in the formatio reticularis, while the fairly slight nonspecific adrenocorticotropic effect of the drug itself can occur when the drug is given half an hour before the neurotropic stress.

Summary

In the present work the effect of both acute and chronic perphenazine treatment on the ACTH release induced by neurotropic stress has been studied. Adrenal ascorbic acid depletion was used as an indicator of the ACTH release. It was found that perphenazine was able in acute experimental conditions to inhibit exceedingly strong adrenal ascorbic acid depletion produced by neurotropic stress although in the perphenazine plus stress group the ascorbic acid content of the adrenals was significantly lower than in the intact controls. When perphenazine was administered daily during a longer period, the drug was no longer able on the ninth day of treatment to prevent the ACTH release and adaptation has thus occurred in this respect. Perphenazine was not able to prevent the adrenal ascorbic acid depletion induced by exogenous ACTH

and pitressin. On the other hand it was observed that the perphenazine treatment in itself caused slight adrenal ascorbic acid depletion. The possible mechanisms of the action of perphenazine on the release of ACTH have been discussed in the light of previous results and those obtained in the present investigation.

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The Effects of Chlorpromazine and Secobarbital on the Reaction Times of Chronic Schizophrenics* ** ***

By

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With 1 Figure in the Text

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The purpose of this experiment was to compare the effects of chlorpromazine and secobarbital, both acute and chronic dosages, on the speed with which schizophrenic patients could respond to a visual stimulus (reaction time, or RT). RT is generally considered a measure of the ability concentrate and attend, or maintain a "set" to respond (SHAKOW 1946).

Previous work by RODNICK and SHAKOW (1940) has shown that the RTs of schizophrenic patients are slower and show greater variability from trial to trial than those of normal subjects. In their study, RODNICK and SHAKOW presented a warning light to their subjects, then, after various preparatory intervals of 1 to 25 seconds, presented a stimulus buzzer to which subjects had to respond by rapidly releasing a previously depressed telegraph key. The preparatory intervals (the length of time between the warning signal and the stimulus to react) were presented under two conditions: a regular procedure, where a number of trials at the same interval were presented consecutively, the subjects knowing when to expect the stimulus and when the intervals would change; and an irregular procedure, where intervals were presented randomly. Normal subjects produced faster RTs on the regular procedure through the 15 second preparatory interval, after which there was no difference between RTs on either procedure. Schizophrenic patients were only able to take advantage of the regular procedure through the four second interval. Schizophrenic patients showed an inability to keep an effective

* This study is a revision of part of a dissertation submitted in partial fulfillment of the requirements for the degree Master of Arts, from the Catholic University of America, August 1957, by the senior author. Thanks are due Dr. JOHN W. STAFFORD, who served as thesis advisor.

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set to respond for more than a few seconds while normals were able to attain a higher level of preparation to react and were able to maintain that set more consistently (SHAKOW 1946).

HUSTON and SENF (1952) indicated that this RT impairment was not specific to schizophrenia. They found the order of RT performance, from worst to best, to be chronic schizophrenics, early schizophrenics, depressives, neurotics, and normals. The schizophrenics tended to be a good deal worse than the other groups.

RODNICK and SHAKOW suggested that a drug which reduced this impaired maintenance of set, particularly in schizophrenics, should lead to improved RT performance. Testing this hypothesis, HUSTON and SINGER (1945) and HUSTON and SENF (1952) found that following acute doses of intravenously administered sodium amytal coupled with amphetamine, schizophrenic patients made faster RTs on the regular procedure through the 8 second interval. Previously they had maintained this set only through the 4 second interval. The drug combination slowed the over-all RTs of all subject groups, but reduced significantly the variability of the chronic schizophrenic's responses. Thus the patient's RTs became more comparable to those of normal subjects.

LEHMANN and HANRAHAN (1954), MARGOLIS (1957) and others have reported that chlorpromazine improves the ability of schizophrenic patients to concentrate. Patients are said to be rendered capable of sustained attention and concentration, a state not existing prior to the medication. On the basis of these experimental and clinical observations, one might predict that chlorpromazine would lead to an improvement of RT performance.

Since secobarbital has many of the same psychomotor properties as sodium amytal (LAYMAN 1940), it too would be predicted to improve RT in schizophrenic patients.

Methods

Twelve cooperative male schizophrenics were selected from the population of a subacute service of the hospital. Mean age 30.1 years (range: 21–40); mean Full Scale WAIS IQ was 99.1 (range: 84–127); mean years of hospitalization was 3.75 (range: 1–11.5); and mean years of schooling was 12.4 (range: 10–16).

Twelve male normal controls, matched for age with the patient group, but with a slightly higher educational level, were selected from the hospital staff. Controls were tested twice, from six to fourteen days apart, and served as a check on the experimental technique

Each schizophrenic subject was tested on "no drug" before and after the study, after single dosages of placebo, and after 100 and 200 mg of both chlorpromazine and secobarbital. Drugs were administered accord-

ing to a 10×12 modified latin square design employed by KORNETSKY and HUMPHRIES (1958). Each drug was given twice and active drugs were balanced on either side of the placebo so that the first and second five days of the study were replicated for each subject. Subjects were tested three days one week, two days the next, for a total of ten test days in four weeks. At least one day intervened between successive drug administrations. Patients did not receive any medications for at least two weeks prior to the start of the experiment.

Drugs were given orally at midday, 90 minutes prior to testing. The "double-blind" procedure was employed. Lunches were withheld to maximize drug effects.

A minimum of one week after the completion of the acute study, subjects were placed on chlorpromazine, secobarbital, or placebo for successive two week periods. All subjects received two weeks of each treatment, according to a latin square design. The first week on either drug, subjects received 100 mg at 8 a.m. and at 8 p.m. for a total daily dose of 200 mg. The second week on either drug subjects received 200 mg at the above times for a total daily dose of 400 mg. Subjects were tested 90 minutes after the morning medication on the fifth day of each week, using the same procedure as on the acute study. Breakfasts were omitted on testing days. With the exception of one subject who became inaccessible during the course of the study, the same subjects were employed on both the chronic and acute RT studies.

Visual RT was recorded to the nearest five milliseconds by means of a Standard Timer. A Hunter Timer was used to vary preparatory intervals between a warning and a stimulus light. The Standard Timer made a slight clicking noise on presentation of the stimulus light, providing the subjects with both auditory and visual cues upon which to base their responses. Intervals were presented under two conditions: an irregular procedure, in which five trials at each of four preparatory intervals (1, 2, 4, and 8 seconds) were presented randomly (different random orders on each test day), and a regular procedure, in which five successive trials were presented at each interval, in the sequence 1, 2, 4, 8. On the regular procedure, subjects were told which interval to expect. Procedures were alternated from day to day to avoid any minor interfering sets (SHAKOW 1946). Subjects were given practice only on the first "no drug" day. Standard instructions were used throughout. Four hundred RTs were obtained from each schizophrenic subject under acute drug and placebo conditions, and 240 RTs under conditions of chronic drug administration. Eighty RTs were obtained from each schizophrenic and normal subject under "no drug" conditions.

Results

A comparison of the RT performance of normal and schizophrenic subjects under no-drug conditions partially supported previous findings. Variances due to individual subjects were so much greater for schizophrenics than for controls that it was not possible to run a combined analysis of variance and analyses of variance were run separately for each group. The normal subjects were able to respond more rapidly on the regular than the irregular procedure through the 4 seconds preparatory interval. Schizophrenics were significantly faster on regular than irregular procedure only at the 1 second interval (see Fig. 1).

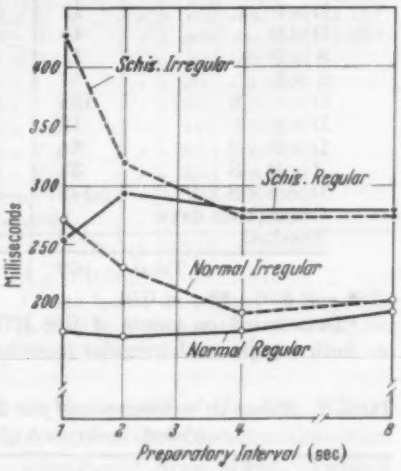

Fig. 1. A comparison of normal and schizophrenic subjects' reaction time at various preparatory intervals

An analysis of variance (EDWARDS 1950) computed on the mean RTs at each interval and procedure for each subject (both days combined) under placebo and "no drug", showed no placebo effect.

The hypothesis that the drugs would lead to an improvement of RT in schizophrenic subjects was tested by an analysis of variance computed on the means of the five RTs at each interval, procedure, and drug day for each subject. Summarized in Table 1, this analysis shows significant drug effect on RT. A correction statistic (epsilon) for repeated observations on the same data (BOX 1954) was applied to the raw df for entry into the F table.

Table 1 indicates that different RTs were obtained under the different procedures at the various intervals, as expected (the Procedures and Intervals main effects, and the Intervals × Precedures interaction in Table 1).

Mean differences between placebo and each of the drugs were compared by the Dunnet test for comparing a series of scores against a standard (DUNNET 1955), and showed no over-all speed differences between placebo and any of the drugs. Mean differences between all drugs were tested by the Scheffé test for making all possible comparisons within a group of scores (STANLEY 1957). Despite a significant F ratio for Drug effect (see Table 1) the only difference with the Scheffé test was between 100 mg of secobarbital and 200 mg of chlorpromazine.

Intra-individual variability under each of the drugs was tested by the Pitman test for correlated variance (KENDALL 1948) comparing

Table 1. *Summary of analysis of variance of schizophrenic RTs under Placebo, 100 and 200 mg of Chlorpromazine and Secobarbital (acute dosages[1])*

Source of variance	*df*	*df* corrected	Mean sq.	*F*
Drugs (D)	4	3	91,347	2.92*
Subjects (S) . . .	11		287,010	
Procedures (P) . .	1		875,679	20.84**
Intervals (I) . . .	3	1	337,198	7.62*
I × P	3	1	320,445	16.51**
D × P	4		21,242	1.60
D × I	12		18,541	0.91
D × S	44	33	31,320	
S × P	11		42,017	
S × I	33	14	44,260	
D × I × S	132		20,309	
D × I × P	12		4,643	0.43
D × P × S	44		13,238	
I × P × S	33	14	19,411	
D × I × S × P . .	132		10,919	
Order (both days) .	1		102,176	6.27**
Residual	479		16,304	
Total	959			

* $p < 0.05$ ** $p < 0.01$

[1] Data based on means of five RTs at each of four preparatory intervals, on both regular and irregular procedures.

Table 2. *Means in milliseconds of five RTs at each interval and procedure, subjects combined, under each of the experimental conditions*

Drug	Procedure	Acute dosages: Intervals (in seconds)			
		1	2	4	8
Placebo	Regular . . .	288	314	271	282
	Irregular . .	470	409	291	263
Chlor. 100	Regular . . .	262	306	282	309
	Irregular . .	444	368	310	293
Chlor. 200	Regular . . .	336	288	322	338
	Irregular . .	492	406	350	318
Secob. 100	Regular . . .	282	278	288	284
	Irregular . .	387	295	279	267
Secob. 200	Regular . . .	321	264	301	284
	Irregular . . .	484	350	342	298

grand mean RTs for each subject, under each of the drugs. There was greater variability under both placebo and 200 mg of chlorpromazine than under 100 mg of secobarbital.

The Drug × Procedure and Drug × Interval Interactions, shown in Table 1, indicate that none of the drugs differentially affected the

regular as compared to the irregular procedures at any of the preparatory intervals. Table 2 shows the grand means under each drug, at each interval and procedure. Though there are some mean differences between regular and irregular procedures at the 4 and 8 second intervals under some of the conditions, none of these differences was statistically significant. Also under several drugs the 1 second interval on the regular procedure yielded faster RTs than the 2 second interval, but none of these differences are statistically significant.

Also, Table 1 indicates significant order effect, the second five days of the experiment yielding slower RTs than the first five days.

Table 3. *Summary of analysis of variance for schizophrenic RTs under Placebo, 100 and 200 mg of Chlorpromazine and Secobarbital (chronic dosages[1])*

Source of variance	*df*	Mean sq.	*F*
Drugs (D) . .	5	52,020	1.03
Subjects (S) . .	10	582,657	18.42**
Procedures (P) .	1	573,450	11.29**
Intervals (I) .	3	251,510	3.52*
I × P	3	316,610	12.37**
D × P	5	37,990	1.74
D × I	15	43,637	1.73*
D × S	50	50,356	1.59*
S × P	10	50,783	
S × I	30	71,380	
D × I × S . .	150	25,275	
D × I × P . .	15	13,969	
D × P × S . .	50	21,870	
I × P × S . .	30	25,603	
Order (days) .	5	11,136	
Residual . . .	145	31,638	
Total	527	47,214	

* $p < 0.05$. ** $p < 0.01$.

[1] Data based on means of five RTs at each of four preparatory intervals, on both regular and irregular procedures.

An analysis of variance computed on the means of the five RTs at each interval, procedure, and drug day, under chronic administration (summarized in Table 3) indicated no significant drug effect. Table 4 shows the grand means under each drug.

Table 4. *Means in milliseconds, of five RTs at each interval and procedure, subjects combined, under each of the experimental conditions*

Drug	Procedure	Chronic dosages: Intervals (in seconds)			
		1	3	4	8
Placebo*	Regular . . .	292	315	291	328
	Irregular . .	548	352	350	296
Chlor. 100	Regular . . .	233	243	304	315
	Irregular . . .	440	441	301	286
Chlor. 200	Regular . . .	256	287	288	335
	Irregular . .	427	459	283	283
Secob. 100	Regular . . .	317	300	314	360
	Irregular . .	526	369	363	367
Secob. 200	Regular . . .	545	311	341	352
	Irregular . .	580	371	329	331

* Means of two placebo days combined

Discussion

On the basis of earlier studies by RODNICK and SHAKOW (1940), SHAKOW (1946), and HUSTON *et al.* (1945, 1952) we hypothesized that the chlorpromazine and secobarbital would (1) speed up RT, (2) decrease intra-individual variability, or (3) change the characteristic relationship between the irregular and regular procedures. Results showed no differences in over-all speed of RTs obtained under conditions of drug as compared to placebo. Only 100 mg. of secobarbital produced less RT intra-individual variability than placebo. The regular-irregular procedure relationship at the longer preparatory intervals (the 4 and 8 second intervals) was not altered by either acute or chronic administration of any of the drugs.

In general, previous reports of normal-schizophrenic differences on RT were supported. However, for the schizophrenic patients, the regular procedure yielded significantly faster RTs only at the 1 second preparatory interval. RODNICK and SHAKOW had reported the 2 second interval at the regular procedure yielded maximal RTs for his patients. The normals made faster RTs through the 4 second interval on the regular procedure, and RODNICK and SHAKOW reported faster RTs through a much longer period (15 second).

The most striking result was the failure of chlorpromazine to improve the RT performance of schizophrenic patients. In spite of reported therapeutic effects of chlorpromazine in psychiatric patients, there is no evidence from this study that the drug allows schizophrenics to respond to various preparatory intervals more like normals. This finding is in harmony with the observations of many workers that chlorpromazine does not alter the "basic schizophrenic process", in BLEULER'S sense of a primary attention defect. It is possible, however, that the sample of schizophrenic subjects used in this study may not have been representative of schizophrenics who do respond behaviorally to the drug but we have no data to this effect. Chlorpromazine does not significantly impair RT, though, as seen in Table 2, the means are in the direction of impairment. There was a tendency, also, for 200 mg of chlorpromazine to produce greater intra-individual variability than placebos.

Our results with the barbiturate are different from those obtained by HUSTON *et al.* (1945, 1952). These investigators used sodium amytal coupled with amphetamine sulphate (benzedrine), and the combination of drugs produces effects which differ from the results of either alone. Also, their route of administration was intravenous while ours was oral. Recently it has been suggested (KLEMMER 1956) that a difference in preparatory intervals can make a difference in obtained RT, and our intervals were not the same as though employed by HUSTON *et al.*

Summary

Twelve male schizophrenics were given a simple visual reaction time test (RT) after single doses and chronic (11 days) administration of chlorpromazine and secobarbital. RT was tested under two conditions: irregular, in which preparatory intervals were presented randomly, and regular, in which the same preparatory intervals were given in consecutive order. Results under single doses indicated that secobarbital reduced intra-individual variability, while chlorpromazine did not significantly affect performance. Results under chronic administration indicated that neither drug had a significant effect on RT performance. These findings are different from those obtained by other investigators who have observed facilitation in schizophrenic psychomotor performance after chlorpromazine, and deficit in performance after barbiturates.

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A Comparative Study of the Effect of Drugs on Activating and Vasomotor Responses Evoked by Midbrain Stimulation: Atropine, Pentobarbital, Chlorpromazine and Chlorpromazine Sulfoxide

By

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With 20 Figures in the Text

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Introduction

The mesencephalon mediates and integrates a wide variety of physiological functions. Stimulation of the midbrain will produce elevation of blood pressure (Kabat *et al.*, 1935), increased resistance of the subcutaneous and visceral vascular beds, decreased resistance of the muscular vasculature (Lindgren, 1955) and activation of the EEG via the "reticular activating system" (Moruzzi and Magoun 1949). The central neuronal pathways over which these changes are mediated are not well understood but it has been proposed that they are mediated over serially connected polysynaptic pathways or over parallel cascading pathways (Scheibel and Scheibel, 1958). The nature of synaptic excitatory and inhibitory processes involved in transmission and integration of activity in these systems has not been clearly demonstrated although it is thought that both adrenergic (Bonvallet *et al.*, 1954) and cholinergic (Rinaldi and Himwich, 1955) mechanisms play a role in the ascending activating systems. The role of acetylcholine, *l*-epinephrine and levarterenol in the peripheral portion of vasomotor pathways descending from the mesencephalon is well established (cf Lindgren, 1955); however, the nature of synaptic processes of the central components of this pathway has not been well characterized.

It is of basic importance to know whether the excitability of central components of various functional systems can be selectively depressed by drugs. One basis of selectivity of drug action upon functional systems might be that of the use by one functional system of a synaptic process not used by other systems. In an effort to provide information on these problems atropine, pentobarbital, chlorpromazine and chlorpromazine sulfoxide were compared with respect to their effects on activation of the EEG and vasomotor responses evoked by stimulation of a single locus in the midbrain. Atropine was employed because of its ability to block

selectively peripheral "muscarinic" synapses and its ability to depress the activating response (RINALDI and HIMWICH, 1955; LONGO, 1956; BRADLEY and KEY, 1958). The role of *l*-epinephrine and levarterenol in the function of the central nervous system remains obscure partly because the effects obtained with these agents vary, producing apparently opposite effects depending on dose, route of administration and time after administration (cf ROTHBALLER, 1959). To provide additional information on the role of adrenergic processes in the central nervous system, chlorpromazine, an agent that has both peripheral adrenergic blocking and potentiating properties, and chlorpromazine sulfoxide, an agent that has predominantly peripheral adrenergic potentiating properties, were compared (MORAN and BUTLER, 1956; MARTIN *et al.*, 1960). Pentobarbital has been reported to selectively depress the ascending reticular formation (ARDUINI and ARDUINI, 1954; FRENCH *et al.*, 1953; KING, 1956); however, no data exist on its relative potency in depressing descending functions regulated by the mesencephalon.

Methods

All experiments were performed on cats ranging in weight from 1.9 to 4.0 kilograms. Operative procedures were carried out under ether anesthesia.

Succinylcholine Immobilized Cat. The trachea was cannulated, polyethylene cannuli were placed in the femoral vein and artery, the temporalis muscles were reflected and a small trephine hole made in the calvarium. Following these operative procedures, animals were immobilized with a slow intravenous infusion of a 0.5 percent solution of succinylcholine and placed on artificial respiration. Body temperature was maintained at 39 ± 1^{0} C with heat lamps. Blood pressure was recorded from the femoral artery using a Statham P 23AA strain gauge transducer and registered on an Offner EEG. The EEG was recorded from dural needle electrodes whose tips were placed along the course of the lateral sulcus, resting over the cortex of either the marginal or the suprasylvian gyrus. The anterior electrode, to be designated as A, was placed 3 to 5 mm behind the sulcus ansatus, the midelectrode B was approximately one centimeter posterior to A, and the posterior electrode C was placed on the occipital pole one centimeter behind B. The EEG obtained from the leads left A to left B was fed into an Offner frequency analyser and the analysis recorded with the EEG.

A concentric bipolar stimulating electrode, made from 22 gauge stainless steel tubing with an insulated copper inner conductor, was placed in the midbrain (H. C., AP O; L $1^{1}/_{2}$; V—$1^{1}/_{2}$) stereotaxically. The position of the electrode tip was established from histological sections of fixed brains in which the tip position was marked by electrocoagulation and staining.

A period of two hours was allowed to elapse between the removal of ether and the beginning of stimulation. The midbrain was stimulated for 10 seconds every five minutes. The onset of stimulation coincided with the beginning of the frequency analyser's 10-second period of analysis. The parameters of stimulation were a 50 c.p.s. square wave of one millisecond duration. Usually six different stimulus strengths were employed (e.g., 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 volts). Each stimulus strength was repeated three times and in randomized order. The effects of stimulation on vasopressor responses evoked by all stimuli were analysed; however, the effect of only one stimulus on the EEG at each stimulating voltage was analysed. Drugs were slowly injected through a cannula in the femoral vein, and washed in with 2 ml of normal saline. The previously described program of stimulation was repeated after each dose of drug. Dose of drug is expressed as the total cumulative amount.

Drugs employed in this study were atropine sulphate, pentobarbital sodium, chlorpromazine hydrochloride, chlorpromazine sulfoxide, and succinylcholine chloride.

Encéphale Isolé Preparation. The encéphale isolé cat was prepared in the same manner as the succinylcholine immobilized cat, except that both vagi were cut and the cord was transected by suction at the C 1 level. No curarizing agent was used. The stimulating and recording procedure was the same as that used for the succinylcholine immobilized cat. Stimulation of the midbrain did not produce any vasomotor or cardiac changes.

Cerveau Isolé Preparation. The cerveau isolé cat was prepared in the same manner as the succinylcholine immobilized cat, except that trephine holes were made bilaterally and an electrolytic lesion was made with a pair of insulated electrodes spaced 3 mm apart and bared for 12 mm from the tip. The lesion was made at H. C. AP 0 in three steps with the tip of the right electrode placed successively at H. C. right L 5, H. C. right L $1^1/_2$, and H. C. left lateral 2 at a depth of H. C. V-7. This procedure produced either a complete transection of the brainstem at the intercollicular level or left only thin connecting filaments on the lateral and inferior aspects of the midbrain. All cats could maintain themselves with spontaneous respiration; however, one of 3 animals was placed on artificial respiration. There was no significant difference in the EEG of the cats respiring spontaneously and the cat on artificial respiration. Needle electrodes were placed in positions A and B bilaterally.

Analysis of data

Stimulation of the medial mesencephalon evoked pressor responses and tachycardia that had a latency of less than three seconds. Upon termination of the stimulus, a marked bradycardia appeared in most preparations if blood pressure rises were greater than 50 mm of Hg. The magnitude of the pressor responses was

calculated as the difference between peak systolic pressure during or immediately after stimulation and the prestimulatory systolic pressure. Increasing strengths of stimulation produced increasingly large pressor responses and the relationship of the magnitude of response to strength of stimulation was characterized by calculating the regression line, using standard statistical procedure, in which stimulus strength was the independent variable and magnitude of pressor responses the dependent variable. All regression lines were calculated from the responses evoked by 12 to 18 stimuli of graded intensity and were significantly linear ($p < 0{,}05$). The intercept of the regression line with the line, response $= 0$, was used as the measure of threshold (excitability) and the slope of the regression line as a measure of reactivity. The effect of drugs on threshold was the mean of the differences between intercept before and after drug determined usually from six or more experiments. The effect of drugs on reactivity was determined by calculating the mean ratio of the slope after drug to the slope before drug for six or more experiments.

Because the vasomotor response had a latency of less than three seconds and all measurements were made within 15 seconds of the onset of stimulation (less than one circulation time) it was presumed that activation of the adrenal medulla played no role in the pressor responses.

To provide a measure of the effect of drugs on reflex bradycardia, the difference in pulse rate for 10-second intervals before stimulation and for a 5-second post-stimulatory interval, encompassing the period of maximum bradycardia, was determined for all pressor responses of 70 to 120 mm of Hg magnitude before and after drug.

Electroencephalograph. The Offner frequency analyser provides a measure of EEG activity, integrated for 10-second periods, for 24 frequency bands (1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 27 and 30 c.p.s.). The activity of any frequency is the amplitude of the analyser pen deflection for a given 10-second interval.

The activity at each of the 24 frequencies was measured for six 10-second epochs prior to stimulation of the midbrain, for the 10-second interval during the stimulation of the midbrain, and for the six 10-second epochs following stimulation. The frequency spectrum for each dose level of each drug was determined from the mean activity of all frequencies during the prestimulatory records. The delta index for each 10-second epoch was defined as the sum of the activity measured at 1.5 through 3.5 c.p.s. Mean delta indices were calculated from the prestimulatory analysed record before and after drug. The increment in delta index is the mean difference between the mean delta index after and before drug. Percent delta index is the ratio of delta index (mean or single epoch) to the mean delta index of the unstimulated undrugged record expressed as percent. The percent delta index was determined for each strength of stimulation of the midbrain, and a regression line was calculated in which stimulus strength was the independent variable and percent delta index was the dependent variable. The slope of the regression line was used as a measure of reactivity of the activating response. Because of the small amount of delta activity in control tracings, it was impossible to obtain a precise and significant measure of reactivity of the activating response in the undrugged succinylcholine immobilized cat. Consequently the reactivity of the activating responses after drug was compared to reactivity of the activating responses in the undrugged encéphale isolé preparation. Threshold in the undrugged succinylcholine immobilized cat was defined as the smallest voltage producing depression of the delta index. Following drug, threshold for the activating response was defined as the intercept of the percent delta index stimulus response curve with the line "percent delta index" = 100. The intercept so calculated was the voltage

necessary to produce a record that had the same quantity of delta activity as the unstimulated control tracing. Thus threshold before and after drug is the voltage necessary to produce comparable functional states. This definition of threshold differs from the classic definition in which threshold is a measure of the strength of stimulation necessary to produce a just perceptible change. The intercepts and slopes so calculated are not to be taken as precise estimates nor are they necessarily indicative of actual state achieved; e.g., stimulating voltages were not always elevated to such a value after 0.4 mg/kg or larger doses of atropine that percent delta index was reduced to control level.

Results

Cerveau Isolé. The EEG of the cerveau isolé preparation showed a predominant spindle pattern (Fig. 2) and produced a frequency spectrum with a large amount of delta activity, a very high peak of activity in the 4 to 13 c.p.s. range, and a large quantity of 20 to 30 c.p.s. activity (Fig. 1). The variability of the cerveau isolé frequency spectrum (standard deviation) was small compared to the variability seen in the frequency spectra of the encéphale isolé and the succinylcholine immobilized cat. Comparing the EEG (Fig. 2) with frequency spectrum (Fig. 1), wave forms can be discerned that are responsible for the activity from $1^1/_2$ to 13 c.p.s. Bursts of low voltage waves from 18 to 45 c.p.s. can be found in the EEG of the cerveau isolé preparation, but their frequency of occurence and amplitude was not appreciably greater than that observed in the EEG of the succinylcholine immobilized cat. A large amount of the activity observed in the 20 to 30 c.p.s. range must result from the harmonic content of lower frequency activity. The spindles are composed of waves with very sharply ascending and descending phases and certainly

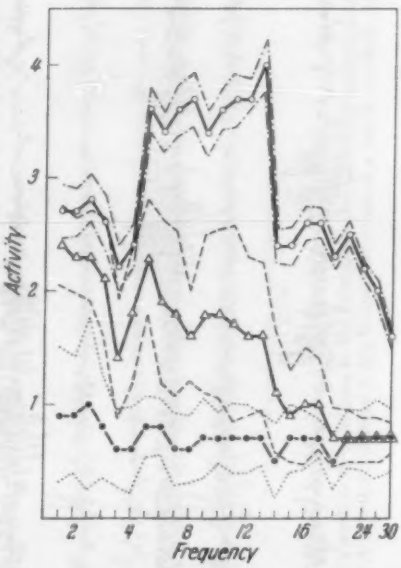

Fig. 1. Frequency spectra of the cerveau isolé, encéphale isolé and succinylcholine immobilized cat Standard deviation of each frequency is indicated by dotted lines for succinylcholine immobilized cats, dashed lines for the encéphale isolé and dash-dot lines for the cerveau isolé preparations. The frequency spectrum for the succinylcholine immobilized preparation was computed from 135 minutes of analyzed record obtained in 27 cats. The frequency spectrum for the encéphale isolé preparation was computed from 31 minutes of analyzed record obtained in 3 cats, while the frequency spectrum for the cerveau isolé preparation was computed from 36 minutes obtained in 3 cats. ● Succinylcholine, △ encéphale isolé, ○ cerveau isolé

Fig. 2. Consecutive portions of a tracing taken from head left A to left B of a cerveau isolé preparation. The frequency spectrum of this short tracing was in all respects similar to the mean frequency spectrum presented in Fig. 1

deviate markedly from a sinusoidal configuration.

Encéphale Isolé. The EEG of the encéphale isolé preparation differed from the cerveau isolé in several respects. It showed a variety of EEG patterns and in some instances these variations had behavioral correlates. When the room was darkened and quiet the EEG was usually synchronized (Fig. 3a), although periods of low voltage high frequently activity occurred and on some occasions the high frequency activity was accompanied by biting movements of the cat. Even in the highly synchronized record, spindle activity was not as regular as in the cerveau isolé preparation and the relative amount of irregular slow-wave activity was greater (Fig. 3a). This variability and greater variety of wave forms were manifested in the frequency spectrum (Fig. 1) by two peaks of approximately equal magnitude; one in the delta range and one in the range of 4 to 13 c.p.s. There was no striking

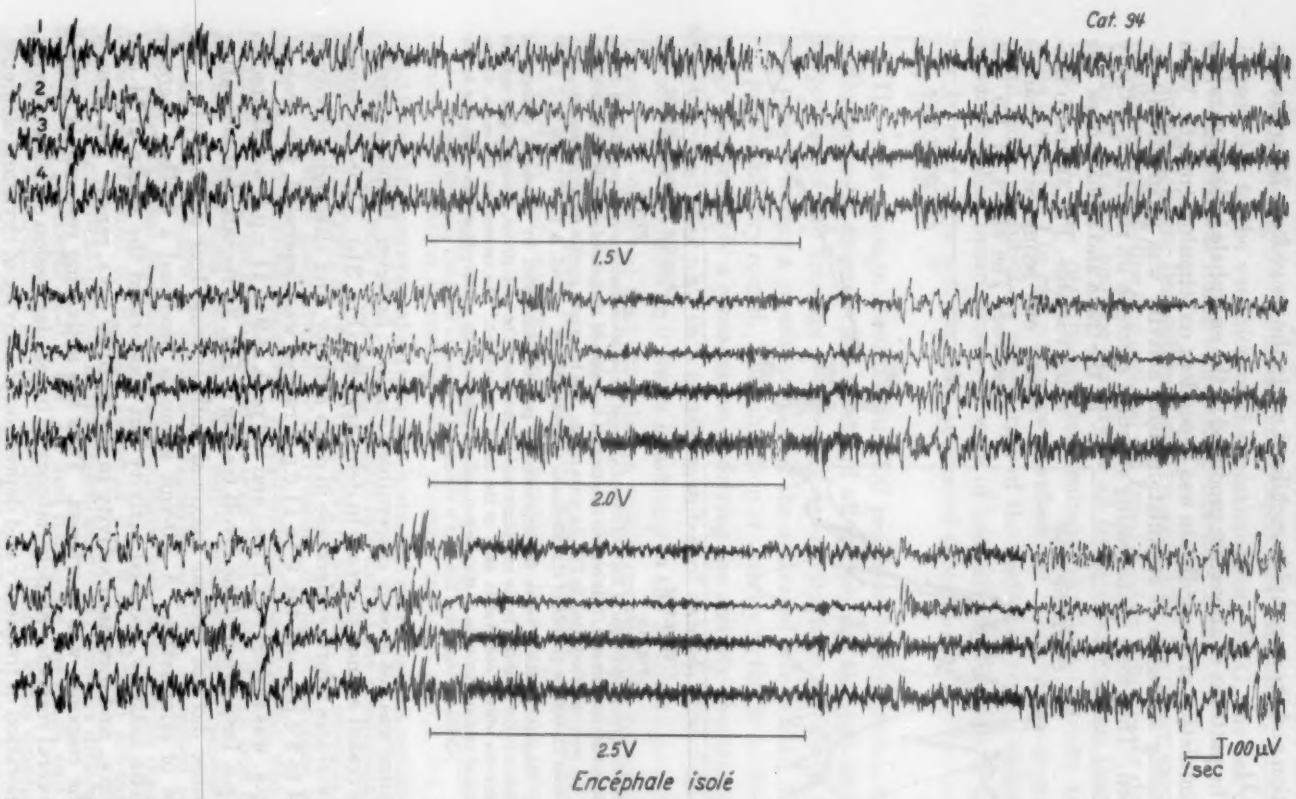

Fig. 3a. The effect of 1.5-, 2.0- and 2.5-volt stimuli to the midbrain on the EEG activation pattern of an encéphale isolé preparation. Channel 1, right A to left C; channel 2, left A to left B; channel 3, left B to left C; channel 4, left A to left C. Channel 2 analysed

difference between the frequency spectrum of the encéphale isolé preparation and the succinyl immobilized cat in the range from 20 to 30 c.p.s. (Fig. 1).

The patterns of alteration produced in the encéphale isolé preparation by stimulation of the midbrain was dependent on stimulus strength. With increasing strengths of stimulation delta activity was progressively depressed. The effect of increasing stimulus strength on rhythmic activity in the theta and alpha ranges was more variable. Fig. 3a and b illustrate one sequence of changes observed. The effect of 1.5 volt

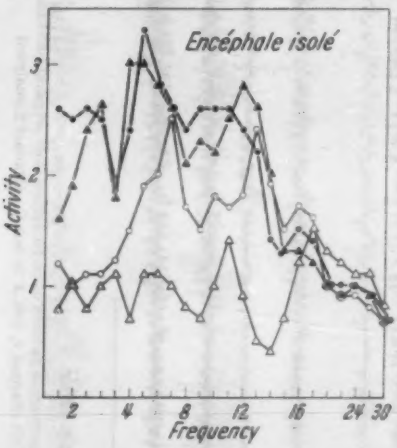

Fig. 3b

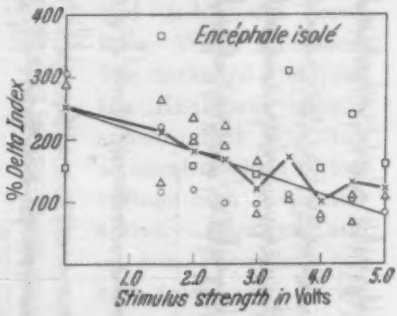

Fig. 4

Fig. 3b. Frequency spectrum of EEG of encéphale isolé preparation during control periods and during stimulation of the midbrain. The control spectrum is the mean of 10 minutes of analyzed record from which the portions illustrated in Fig. 3a were taken. The frequency spectra for $1^1/_2$, 2, and $2^1/_2$ volts were taken during the periods of stimulation to the midbrain. ● control, ▲ 1.5 V, ○ 2.0 V, △ 2.5 V

Fig. 4. Stimulus response curve for depression of percent delta index by increasing strength of stimulation to the midbrain in the encéphale isolé preparation. The open circles, triangles, and squares designate the effects observed in each of the three cats studied. The crosses are the mean values obtained at various strengths of stimulation and are connected by a heavy line. The light line is the calculated regression line and is significantly linear to the 0.005 probability level

stimulus was not grossly discernible (Fig. 3a); however, frequency analysis revealed a small decrease in delta activity (Fig. 3b). A 2.0-volt stimulus produces a further decrease in delta activity, and although activity in the 4 to 8 c.p.s. and the 9 to 11 c.p.s. ranges was depressed, the peak at 5 c.p.s. was shifted to 7 c.p.s., and the peak at 9 to 11 c.p.s. was shifted to 13 c.p.s. Inspection of the 2-volt tracing of Fig. 3a reveals that activating response did not become maximal until at least four seconds after the onset of stimulation. A 3.0-volt stimulus produced a further decrease in delta activity, reduced activity but accelerated the peaks to 11 and 17 c.p.s., and increased activity in the 20 to 30 c.p.s. range. The latency of the response was shortened. Thus the activating response is graded in several respects; namely, latency of onset, depression of delta activity, acceleration of frequency and depression of activity of rhythmic elements.

Fig. 4 illustrates the progressive decrease in percent delta index by increasing strength of stimulation. Despite the variability, which was in part due to the variation of the prestimulatory EEG, the calculated regression line was linear to a 0.005 probability level.

Succinylcholine Immobilized Cat. The mean EEG frequency spectrum of the succinylcholine immobilized cat failed to show any clearly defined peaks of activity, and the activity at all frequencies was less than one (Fig. 1). In some experiments predominant rhythmic activity in the delta and in the 4 to 14 c.p.s. range was observed. The changes in percent delta index produced by stimulation of the midbrain in the undrugged succinylcholine immobilized cat were of necessity small because of the low level of delta activity, and precluded determining reactivity with any precision.

The most common alteration in EEG produced by stimulation of the midbrain was a decrease in activity of all frequencies through 30 c.p.s. Inspection of the tracings revealed that activity from 30 to 45 c.p.s. was present during a greater portion of the activated record than during the prestimulatory record. The inhibition of activity in the 20 to 30 c.p.s. range was probably a consequence of driving the activity at a frequency range beyond 30 c.p.s. In a smaller number of animals stimulation of the midbrain produced an increase in activity in the 20 to 30 c.p.s. range. It was also observed that stimulation would occasionally increase the activity in the 4 to 8 c.p.s. range. This is illustrated in lead 2 of the control tracing of Fig. 6, where 5 c.p.s. activity was enhanced. This suggested that perhaps delta activity may, on occasions, be accelerated into the theta range.

Atropine Sulfate. *Vasomotor Responses.* Atropine did not produce any significant alteration in resting blood pressure in doses of 0.2, 0.4, 1.0, and 5.0 mg/kg; however, at all dose levels studied it produced a significant increase in heart rate (Table 1). The heart rate during the prestimulatory period was maximally elevated by 0.2 mg/kg of atropine. In animals that showed a marked poststimulatory bradycardia, 0.2 mg of atropine abolished the bradycardia; however, poststimulatory tachycardia was not maximal in some preparations until a dose level of 0.4 mg/kg had been attained. Using both pulse rate and reflex bradycardia to pressor responses as a measure of atropine's vagolytic activity, it would seem that near maximal blockade of vagal outflow was present with dosages of between 0.2 and 0.4 mg/kg. Doses of 0.2, 0.4, 1.0, and 5.0 mg/kg produce a significant increase in threshold (intercept), but the difference between the intercepts at 0.2, 0.4, 1.0 and 5.0 mg/kg was small and not statistically significant (Fig. 20). Atropine in all dose levels employed increased the slope of the stimulus response curve (reactivity), however,

there was no significant difference between the reactivity at the 0.2, 0.4, 1.0 and 5 mg/kg dose levels.

EEG. The frequency spectrum of the EEG revealed that with large doses of atropine (0.4 to 5.0 mg/kg) activity was maximal at 1.5 c.p.s. and decreased with increasing frequencies (Fig. 5). The quantity of 24 to 30 c.p.s. activity was either unaffected or slightly decreased by all dose levels employed.

Table 1

The effects of atropine sulfate, pentobarbital sodium, chlorpromazine hydrochloride and chlorpromazine sulfoxide on resting systolic blood pressure (BP—mm of Hg), resting pulse rate (PR—beats/min.) and reflex bradycardia (CS—beats/min.) in the succinylcholine immobilized cat.

	Control	Atropine Sulfate			
		0.2 mg/kg	0.4 mg/kg	1.0 mg/kg	5.0 mg/kg
BP	162	157	160	162	169
HR	200	240*	252*	240*	250*
CS	−64	+11	+14	+18	
	Control	Pentobarbital Na			
		4 mg/kg	8 mg/kg	12 mg/kg	
BP	151	170*	159*	157	
HR	210	216	220	227	
CS	−89	−135	−126		
	Control	Chlorpromazine HCl			
		1 mg/kg	5 mg/kg	10 mg/kg	
BP	182	139*	135*	129*	
PR	216	236*	229	198	
CS	−110	−115	−109	−110	
	Control	Chlorpromazine Sulfoxide			
		5 mg/kg	15 mg/kg	25 mg/kg	
BP	168	164	157	163	
PR	224	212*	211*	204*	
CS	−71	−74	−82	−51	

* Asterisk indicates value is significantly ($P < 0.05$) different from control value.

In confirmation of earlier studies in dogs (WIKLER, 1952) atropine produces a spindle slow wave pattern; however, the relative proportion of delta to alpha activity was greater following atropine in the cat than following any of the other drugs employed.

Atropine in a dose level of 0.4 mg/kg produced near maximal changes in the EEG frequency spectrum (Fig. 5) and near maximal elevation of delta index (Fig. 20). Atropine, in a dose level of 0.2 mg/kg, produced a marked slow wave pattern in some animals, but in one animal, which was the only one of the series to show a persistent alpha pattern during the control period, atropine (0.2 mg/kg) decreased the regularity of the spindle pattern (Fig. 6). In this experiment as well as in two other experiments in which the control tracing showed a predominantly low voltage fast wave pattern, 0.2 mg/kg of atropine caused the appearance of occasional waves of 0.2 to 0.3 seconds duration and of 100 to 200 microvolts amplitude without producing a highly synchronized EEG.

These waves appeared to be the first consistent sign of atropine activity. In the remaining animals 0.2 mg/kg of atropine produced a record that was qualitatively similar to the prestimulatory record shown in Fig. 7a.

Fig. 6 and 7a illustrate the effects of increasing doses of atropine, and increasing strengths of stimulation in the atropine treated cat, on the activating response. Attention is called to the similarity of the activating response evoked by a 4-volt stimulus to the midbrain following 0.4 mg/kg (Fig. 7a) and 1.0 mg/kg (Fig. 6) of atropine. The predominant effect of activation on the atropine frequency spectrum was to decrease delta activity and to a lesser extent all activity in the range from 4 to 17 c.p.s. (Fig. 7b). Alpha activity was depressed by increasing strength of stimulation and activity of 17 to 30 c.p.s. was either unchanged or slightly decreased.

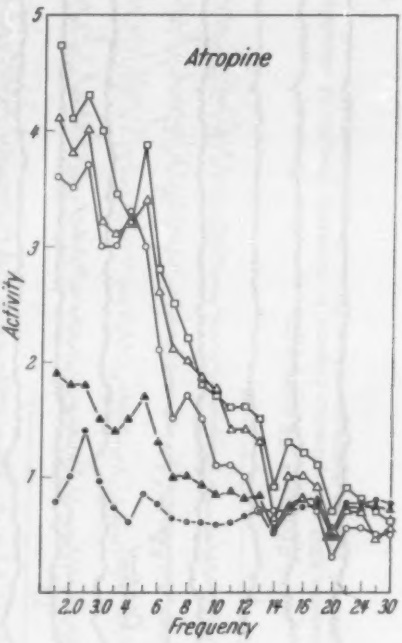

Fig. 5. The frequency spectra of the succinylcholine immobilized cat before and after graded cumulative doses of atropine. The control frequency spectrum, as well as the frequency spectra after 0.2 and 1.0 mg/kg, were computed from 33 minutes of analyzed record obtained from 7 cats. The frequency spectra for the 0.4 mg/kg and 5 mg dose level represents 18 and 10 minutes respectively of analyzed record obtained in three experiments. ● Control, ▲ 0.2 mg/kg, ○ 0.4 mg/kg, △ 1.0 mg/kg, □ 5.0mg/kg

Fig. 8 illustrates the effect of increasing strengths of stimulation on percent delta index following 0.2, 0.4 and 1.0 mg/kg of atropine observed in 3 preparations exhibiting approximately equal sensitivity to stimulation of the midbrain. Several features should be noted: (1) 0.2 and 0.4 mg/kg of atropine caused progressive increases in delta percent while the effect of 1.0 mg/kg was only slightly greater than the 0.4 mg/kg dose level, (2) with all doses of atropine, increasing strength of stimulation produced a decrease in delta index, and (3) the slope of the stimulus response was greater after 0.4 and 1.0 mg/kg than after 0.2 mg/kg of atropine. The increase in reactivity was not solely due to the increase in delta activity, since the ratio of slope to delta percent was greater with all doses of atropine than for the encéphale isolé preparation (Table 2).

Pentobarbital. *Vasomotor Responses.* Pentobarbital in doses of 4 and 8 mg/kg produced a significant increase in the blood pressure and a

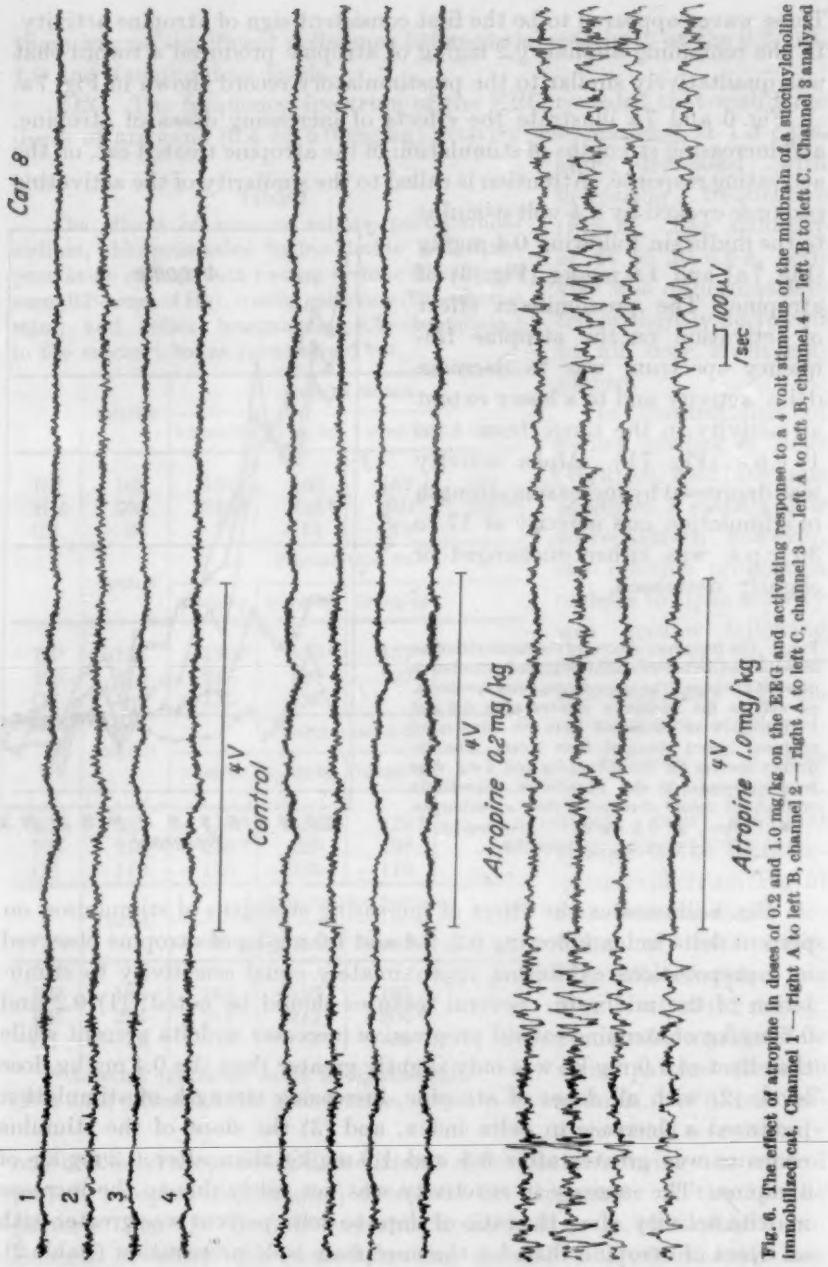

Fig. 6. The effect of atropine in doses of 0.2 and 1.0 mg/kg on the EEG and activating response to a 4 volt stimulus of the midbrain of a succinylcholine immobilized cat. Channel 1 — right A to left B, channel 2 — right A to left C, channel 3 — left A to left B, channel 4 — left B to left C. Channel 3 analyzed

small increase in the pulse rate of the succinylcholine immobilized cat (Table 1), and did not decrease the magnitude of reflex bradycardia. The

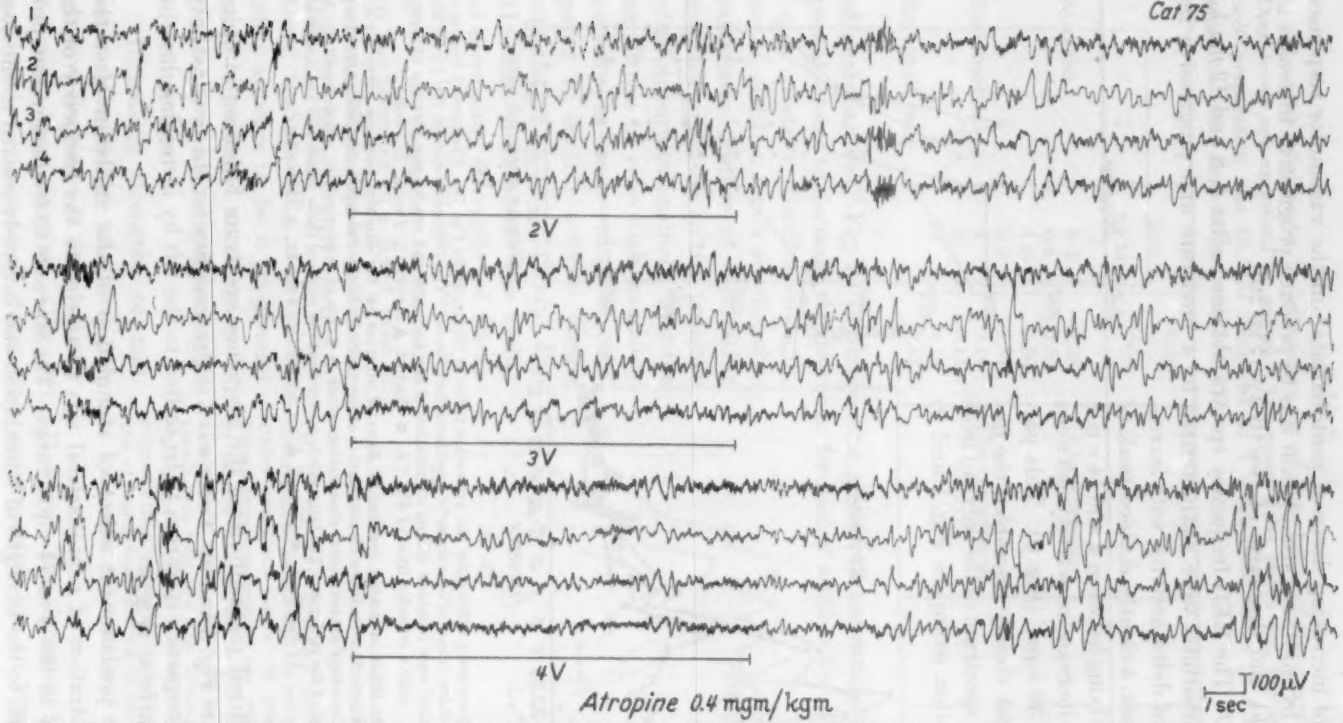

Fig. 7a. The effect of 0.4 mg/kg of atropine on the spontaneous EEG and activating response to increasing strengths of stimulation to the midbrain of a succinylcholine immobilized cat. Channel designation same as Fig. 6. Channel 3 analyzed

effects of increasing doses of pentobarbital on the vasomotor responses evoked by midbrain stimulation was to produce progressive increases in threshold and decreases of reactivity (Fig. 20).

EEG. The EEG frequency spectra obtained after 4, 8 and 12 mg/kg of pentobarbital were characterized by a moderate and progressive increase of delta activity with increasing doses, a clearly defined peak of activity lying between 4 and 14 c.p.s. and an increase in activity between 15 and 30 c.p.s. (Fig. 9). This pattern most closely resembled the frequency spectrum of the cerveau isolé preparation (compare Fig. 1 and 9)

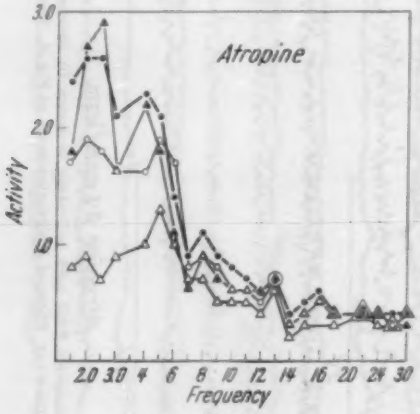

Fig. 7b

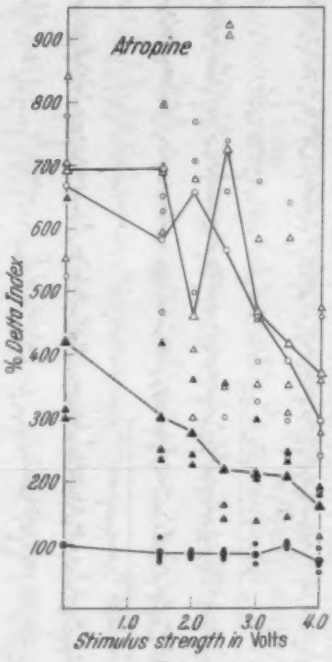

Fig. 8

Fig. 7b. Frequency spectra for the activation patterns illustrated in Fig. 7a. The control frequency spectrum is the mean of 6 minutes of prestimulatory record. The frequency spectra for 2-, 3-, and 4-volt stimuli were obtained during stimulation of the midbrain and are for the portions of record above stimulus lines of Fig. 7a. ● Control, ▲ 2 volts, ○ 3 volts, △ 4 volts

Fig. 8. The effect of graded cumulative doses of atropine on the stimulus response curve for depression of percent delta index by stimulation of the midbrain in the succinylcholine immobilized cat. The small symbols are individual observations made in 3 cats of approximately equal sensitivity to stimulation of the midbrain. The large symbols represent the mean of these values and are connected by fine lines. ● Control, ▲ 0.2 mg/kg, ○ 0.4 mg/kg, △ 1.0 mg/kg

and differed markedly from the frequency spectrum following atropine (compare Fig. 5 and 9). There was a slight tendency for the peak activity of the frequency spectrum to be shifted to the left by increasing doses of pentobarbital (Fig. 9).

The predominant effect of stimulation of the midbrain after the administration of pentobarbital was to accelerate the frequency of the activity in the 4 to 14 c.p.s. range. The increase in frequency was proportional to the strength of stimulation and inversely related to the dose

Table 2

The ratio of slope to % delta index for all dose levels of the drugs studied. Dose levels are expressed in mg/kg. The mean delta index for the encéphale isolé preparation was 10.5 as compared to a mean delta index of 4.2 for the succinylcholine immobilized cat.

	Dose mg/kg	Slope / % δ-Index		Dose mg/kg	Slope / % δ-Index
Atropine	0.2	0.28	Chlorpromazine	1	0.27
	0.4	0.52		5	0.28
	1.0	0.30		10	0.30
	5.0	0.34			
Pentobarbital . .	4	0.14	Chlorpromazine	5	0.38
	8	0.11	sulfoxide	15	0.48
	12	0.14		25	0.38
Encéphale isolé .		0.13			

of pentobarbital. Fig. 10 illustrates the ability of increasing doses of pentobarbital to decrease the degree of frequency acceleration produced by a constant stimulus strength, but in addition shows another characteristic feature of activating responses induced in the presence of pentobarbital; namely, that the amplitude of even high frequency activity is much enhanced compared to control activity during stimulation of the midbrain. Fig. 11a and b illustrate the ability of increasing strengths of stimulation to produce increasing degrees of frequency acceleration in the presence of a fixed dose of pentobarbital. The frequency analysis of the activated portion of these tracings (Fig. 11b) shows what appears to be a progressive and continuous acceleration of frequency with increasing strengths of stimulation.

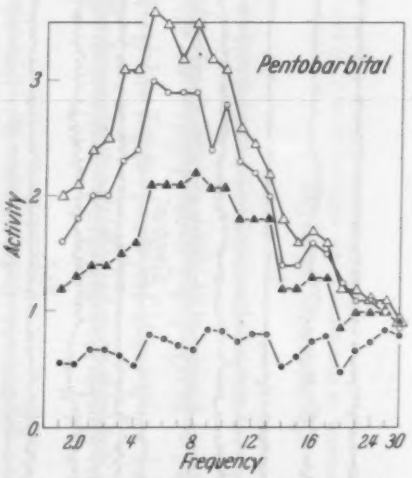

Fig. 9. The EEG frequency spectra of the succinylcholine immobilized cat before and after graded cumulative doses of pentobarbital. Control frequency spectrum was computed for 33 minutes of analyzed record obtained in 7 animals, 4 mg/kg and 8 mg/kg frequency spectra were computed from 37 minutes of analyzed record obtained in 7 cats while the 12 mg/kg frequency spectrum was computed from 32 minutes of record obtained in 6 animals. ● Control, ▲ 4 mg/kg, ○ 8 mg/kg, △ 12 mg/kg

Increasing strengths of midbrain stimulation produced progressive decreases in delta activity following pentobarbital (Fig. 12). However the increase in slope produced by increasing doses was accompanied by an increase in

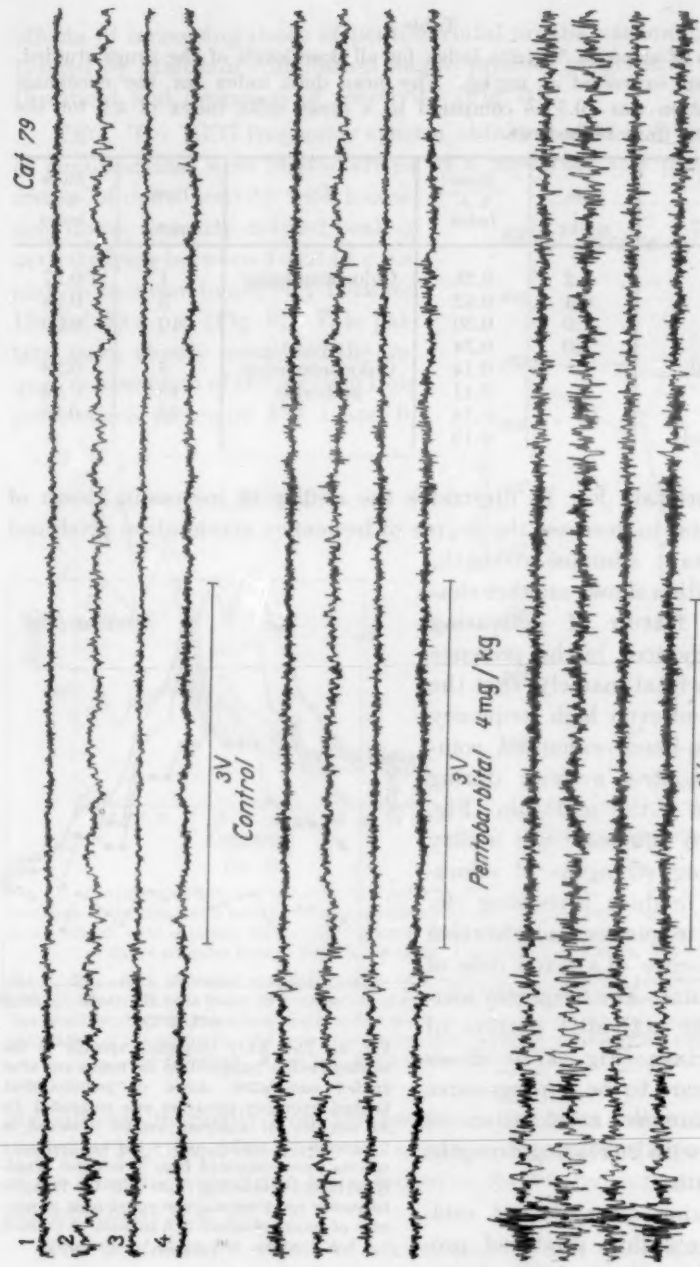

Fig. 10. The effect of 4 and 12 mg/kg of pentobarbital on spontaneous EEG and activating response evoked by a fixed stimulus voltage to the midbrain. EEG is recorded from the same leads as in Fig. 6. Channel 3 analyzed

delta activity, and the ratio of slope to increase in delta activity was essentially unchanged by increasing doses of pentobarbital and

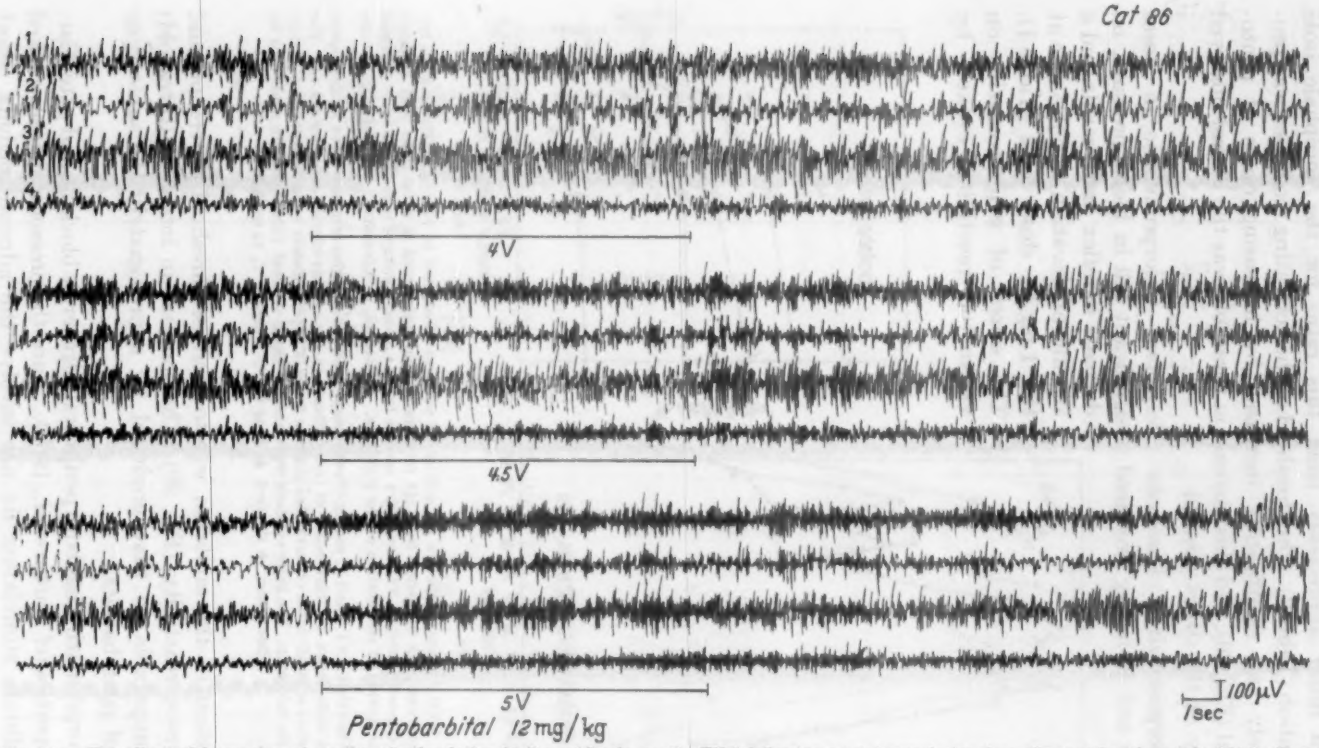

Fig. 11a. The effect of increasing strengths of stimulation to the midbrain on the EEG following a total cumulative dose of 12 mg/kg of pentobarbital. Channel designation same as Fig. 6. Channel 3 analyzed

did not differ appreciably from this ratio for the encéphale isolé preparation (Table 2). The threshold of the activating responses was progressively and significantly increased by increasing doses of pentobarbital (Fig. 20), and this increase in threshold was the largest observed for any of the drugs studied.

Chlorpromazine. *Vasomotor Responses.* Chlorpromazine in doses of 1, 5 and 10 mg/kg produced a significant fall in blood pressure, no decrease in reflex bradycardia and a significant elevation of pulse rate at the 1 mg/kg dose level (Table 1). The effect of chlorpromazine on vasomotor reactivity evoked by

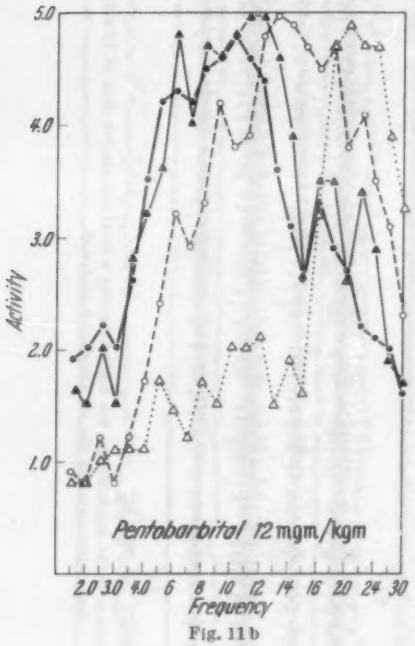

Fig. 11b

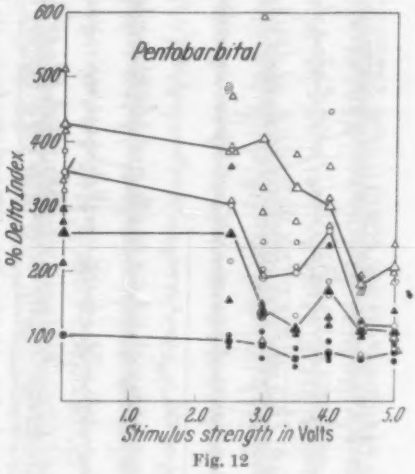

Fig. 12

Fig. 11b. EEG frequency spectra for activation patterns illustrated in Fig. 11a. The control frequency spectrum was computed from six minutes of analyzed record in a cat that had received 12 mg/kg of pentobarbital. The frequency spectra for 4, 4.5 and 5 volts of stimulation were obtained during the period of stimulation of the midbrain. ● Control, ▲ 4.0 volts, ○ 4.5 volts, △ 5 volts

Fig. 12. The effects of 4, 8 and 12 mg/kg of pentobarbital on the stimulus response curve for depression of percent delta index by stimulation of the midbrain in the succinylcholine immobilized cat. The small symbols are individual observations made in 3 cats of approximately equal sensitivity to stimulation of the midbrain. The large symbols represent the mean of these values and are connected by fine lines. ● Control, ▲ 4 mg/kg, ○ 8 mg/kg, △ 12 mg/kg

stimulation of the midbrain was to increase threshold (intercept) and to decrease reactivity (Fig. 20). The increase in intercept (threshold) was comparable to that produced by approximately the same dose levels of pentobarbital.

Chlorpromazine has both peripheral adrenergic blocking and potentiating properties (cf Martin *et al.*, 1960). Since the pressor responses evoked by midbrain stimulation do not involve the adrenal medulla (short

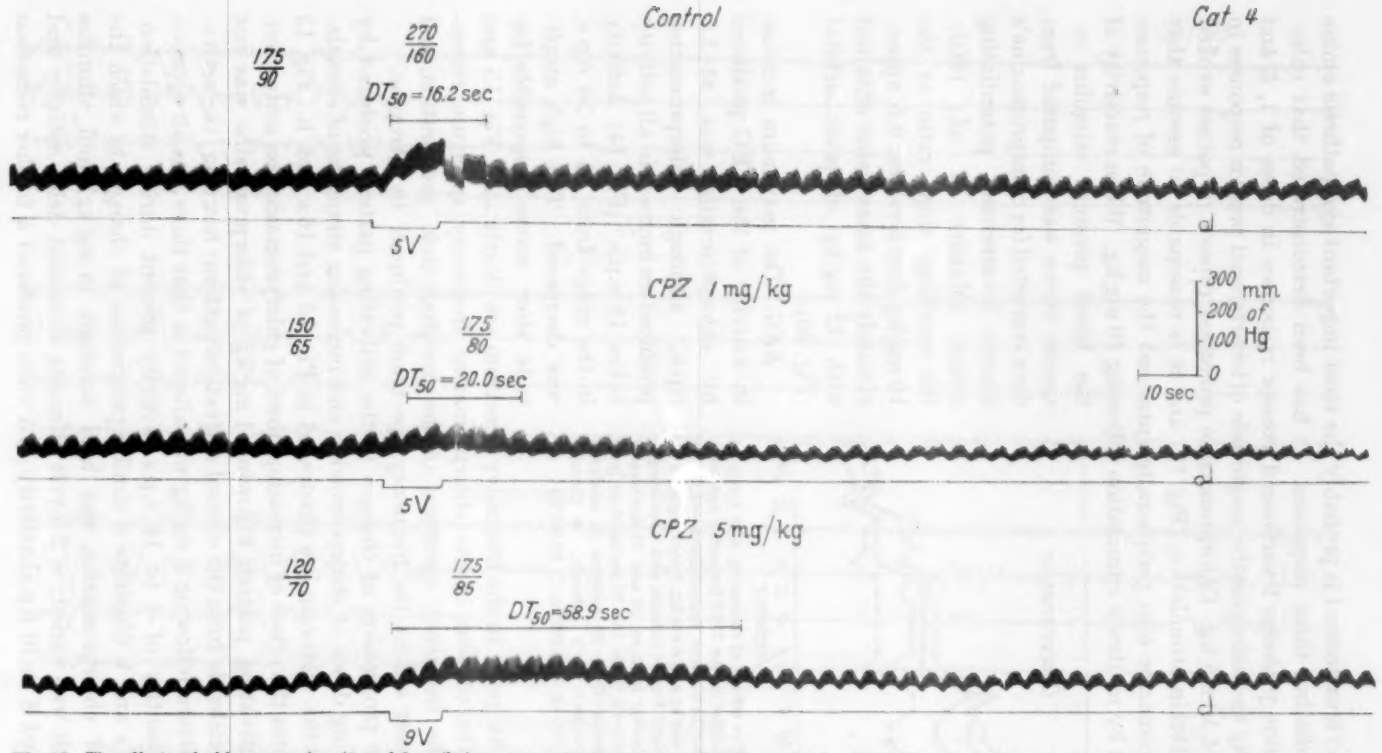

Fig. 13. The effects of chlorpromazine (1 and 5 mg/kg) on vasomotor responses evoked by midbrain stimulation. 1 and 5 mg/kg produced progressive depression of the blood pressure response. In addition these dose levels prolonged the duration of the pressor response. A stimulus strength of 5 volts produced a blood pressure elevation of 95 mm of Hg with a decay time$_{50}$ of 16.2 seconds in the untreated animal. Following 5 mg/kg of chlorpromazine a 9-volt stimulus produced a blood pressure rise of 55 mm of Hg with a decay time$_{50}$ of 58.9 seconds

latency) levarterenol is probably the most important sympathetic amine for mediating these responses. It has been demonstrated that chlorpromazine prolongs levarterenol pressor responses in doses of 1, 5 and 10 mg/kg and enhances the magnitude of levarterenol pressor responses in doses of 10 mg/kg. Chlorpromazine prolonged pressor responses evoked by midbrain stimulation (Fig. 13) and it is reasonable to assume that chlorpromazine also peripherally enhanced the magnitude of responses evoked by midbrain stimulation following 10 mg/kg. When reactivity of the blood pressure stimulus response curve was computed from data corrected for chlorpromazine's known levarterenol potentiating action (MARTIN *et al.*, 1960), the resulting slope ratio at the 10 mg/kg-dose level was 0.5, approximately the same value obtained with 12 mg/kg of pentobarbital (Fig. 20).

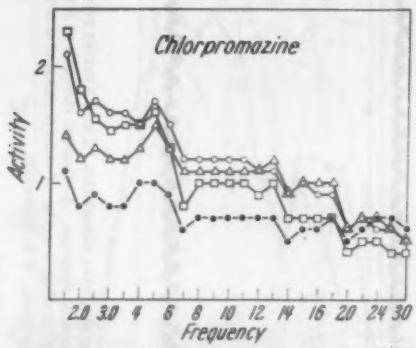

Fig. 14. The effects of increasing dose levels of chlorpromazine on the EEG frequency spectrum of the succinylcholine immobilized cat. The control, 1 mg/kg and 5 mg/kg, frequency spectra were obtained from 6 animals and were computed respectively from 34, 36 and 32 minutes of analyzed record while the 10 mg/kg dose level was computed from 20 minutes of analyzed record obtained in 3 animals. ● Control, △ 1 mg/kg, ○ 5 mg/kg, □ 10 mg/kg

EEG. The maximum increase in activity of the EEG produced by chlorpromazine was at 1.5 c.p.s., although chlorpromazine produced an increase in all activity below 18 c.p.s. (Fig. 14). Activity in the range from 24 to 30 c.p.s. was decreased. The high amplitude slow waves responsible for the delta peak in the frequency spectrum are clearly seen Fig. 15 and 16a. The contour of the chlorpromazine frequency spectrum resembled the frequency spectrum of the encéphale isolé preparation, and to a lesser extent the frequency spectrum produced by atropine.

The progression of changes in the activating pattern produced by increasing doses of chlorpromazine and increasing strengths of stimulation to the midbrain are illustrated in Fig. 15 and 16a and b. Fig. 15 illustrates the effect of increasing doses of chlorpromazine on activation. The activation pattern following 1 mg/kg of chlorpromazine was not distinguishable from the control activation pattern; however, the activation pattern following 5 mg/kg was altered in that there was an appreciable quantity of 8 to 14 c.p.s. activity present during stimulation. Fig. 16a and b illustrate a similar progression of changes in which the dose of chlorpromazine was held constant (5 mg/kg) and stimulus strength was varied; a 2.5-volt stimulus decreased delta activity and enhanced 8 to 16 c.p.s. activity; 3.5 volts produced a further reduction

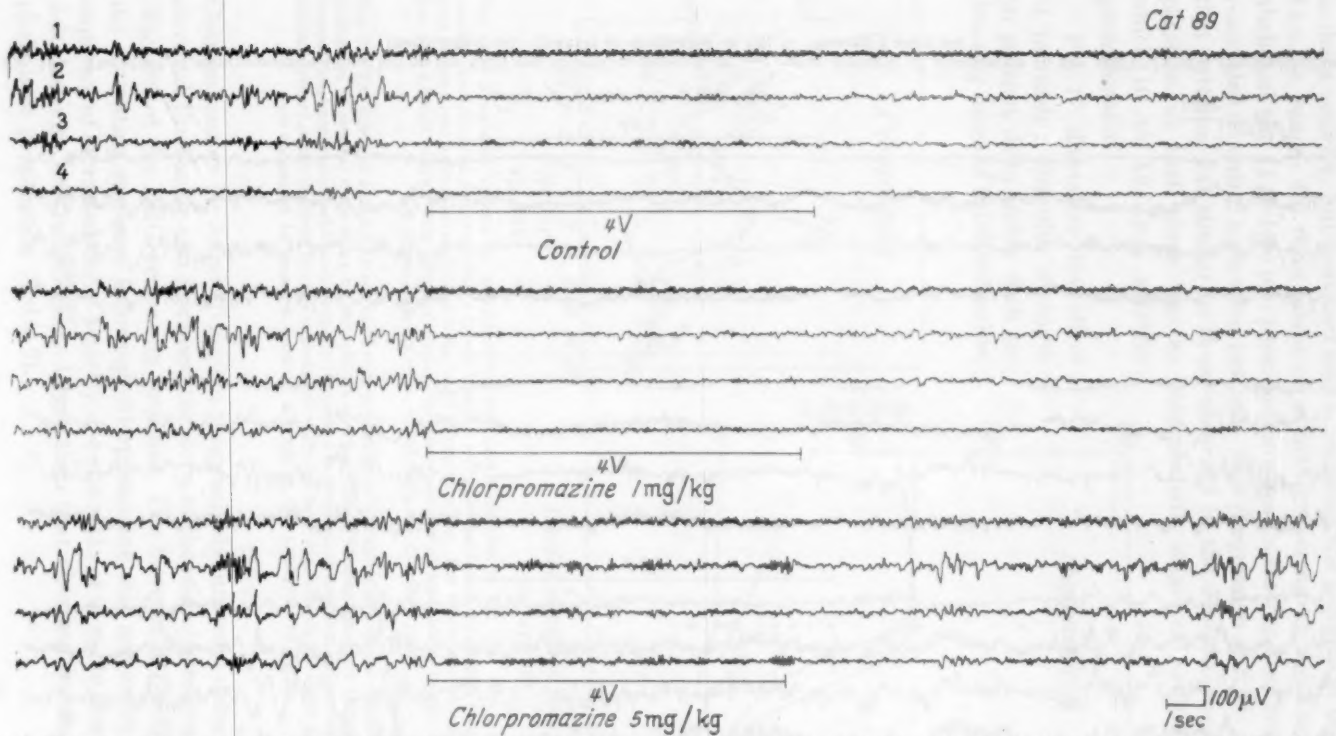

Fig. 15. The effect of chlorpromazine (1 and 5 mg/kg) on the EEG and the activating response evoked by a constant stimulus strength to the midbrain of a succinylcholine immobilized cat. Channels are the same as in Fig. 6. Channel 3 analyzed

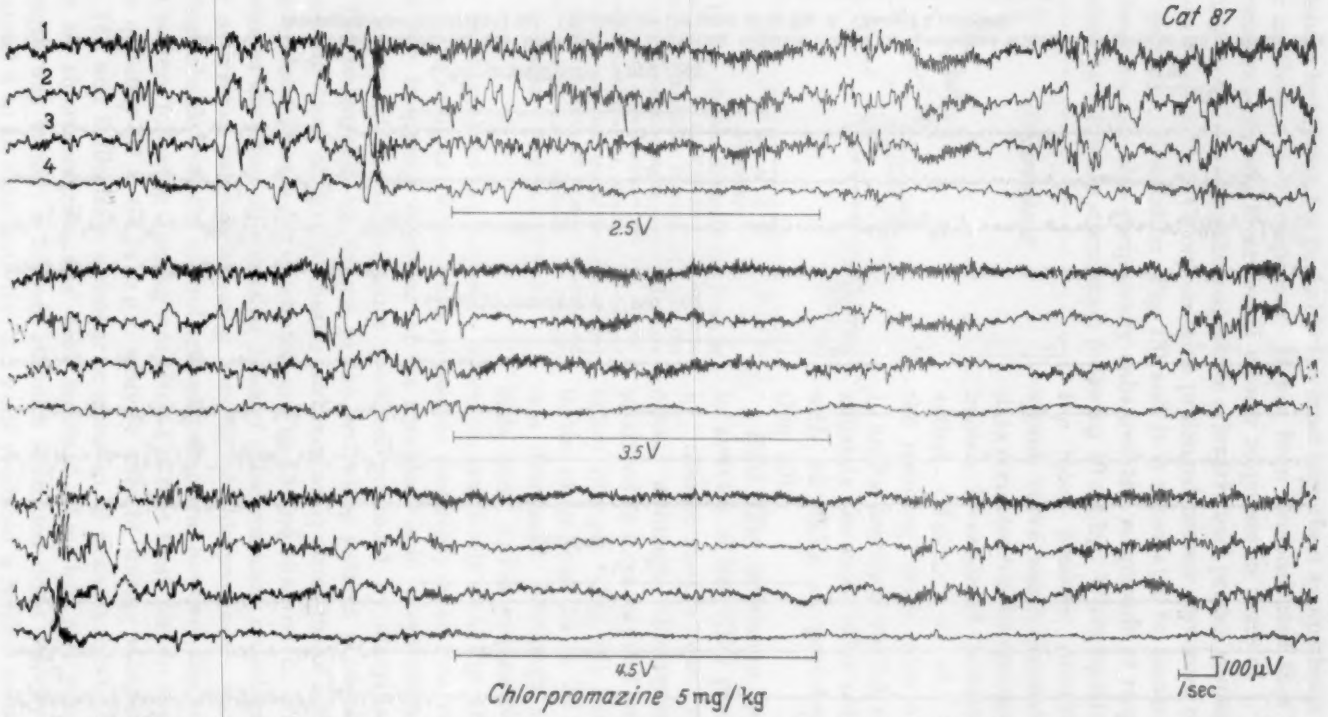

Fig. 16a. The effect of chlorpromazine (5 mg/kg) on the EEG and activating response to increasing strength of stimulation to the midbrain of a succinylcholine immobilized cat. Channel as designated in Fig. 6. Channel 3 analyzed

in delta activity, but increased and accelerated the activity in the 11 to 15 c.p.s. range; 4.5 volts produced a further decrease in delta activity, abolished the 11 to 15 c.p.s. peak and produced a tracing that markedly resembled a control activation pattern. This progression of EEG activation patterns was similar to those observed in the encéphale isolé preparation in that there was an intermediate stage of activation in which 10 to 15 c.p.s. activity predominated.

Fig. 17 illustrates the effect of increasing stimulus strength on percent delta index with increasing doses of chlorpromazine.

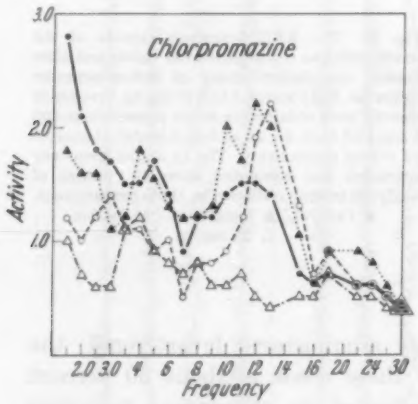

Fig. 16b

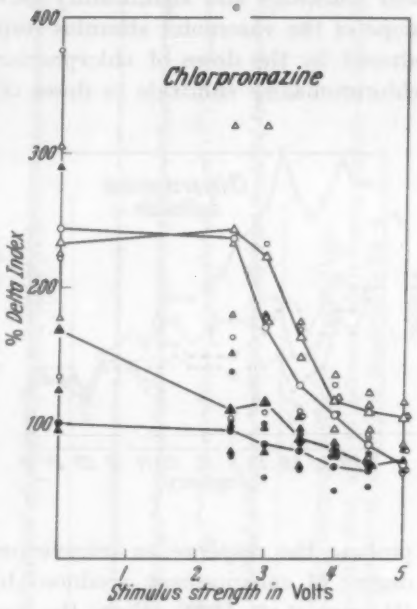

Fig. 17

Fig. 16b. Frequency spectra for the activating responses illustrated in Fig. 16a. The control frequency spectrum was computed from a prestimulatory record of 6 minutes duration in a preparation that had received a cumulative dose of 5 mg/kg of chlorpromazine. The frequency spectra for 2.5-, 3.5- and 4.5-volt stimuli were obtained during the 10-sec. period of stimulation to the midbrain. ● Control, ▲ 2.5 volts, ○ 3.5 volts, 4.5 △ volts

Fig. 17. The effect of 1, 5 and 10 mg/kg of chlorpromazine on the stimulus response relationship for depression of percent delta index by stimulation of the midbrain obtained in three succinylcholine immobilized preparations which were equally responsive to midbrain stimulation. The small symbols indicate observations obtained in each experiment while the large symbols are the mean values and are connected by lines. ● Control, ▲ 1 mg/kg, ○ 5 mg/kg, △ 10 mg/kg

Chlorpromazine (1, 5 and 10 mg/kg) progressively increased delta index, elevated threshold, and increased the slope of the stimulus response line (Fig. 20) of the EEG activating response. The increase in reactivity of the activating response following chlorpromazine was not solely a consequence of increased delta activity, for the ratio of slope to increase in delta activity was considerably larger than that obtained for the encéphale isolé preparation (Table 2).

Chlorpromazine Sulfoxide. *Vasomotor Responses.* Chlorpromazine sulfoxide (5, 15 and 25 mg/kg) produced a small but non-significant decrease in blood pressure, and a small but significant decrease in heart rate. The dose levels employed did not depress reflex bradycardia (Table 1). Threshold for vasomotor responses evoked by midbrain stimulation were slightly elevated by 5 and 15 mg/kg of chlorpromazine sulfoxide and markedly and significantly elevated by 25 mg/kg (Fig. 20). The slope of the vasomotor stimulus response curves were not significantly altered by the doses of chlorpromazine sulfoxide employed; however, chlorpromazine sulfoxide in doses of 5, 10 and 20 mg/kg enhance and

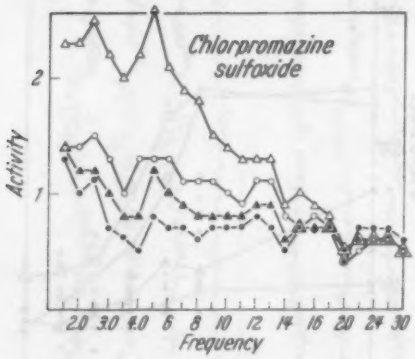

Fig. 18. The EEG frequency spectra of the succinylcholine immobilized cat before and after graded cumulative doses of chlorpromazine sulfoxide. The control, 5 and 25 mg/kg, frequency spectra were obtained in seven preparations and computed from 35, 37 and 39 minutes of analyzed record respectively. The 15 mg/kg frequency spectrum was computed from 19 minutes of analyzed tracing obtained in three preparations. ● Control, ▲ 5 mg/kg, ○ 15 mg/kg, △ 25 mg/kg

prolong the response to intravenously administered levarterenol; the degree of enhancement produced by these doses is about 50 percent (MARTIN *et al.*, 1960). Since the duration of the vasopressor responses evoked by midbrain stimulation (particularly when reflex bradycardia was minimal) were markedly prolonged following chlorpromazine sulfoxide, it is reasonable to infer that the pressor responses may also have been potentiated peripherally by chlorpromazine sulfoxide. Correction of the evoked pressor responses at all dose levels for the peripheral potentiating action of chlorpromazine sulfoxide (multiplied by 0.66) yielded stimulus response curves with slopes significantly lower than control curves for all dose levels.

EEG. The changes in the frequency spectra produced by chlorpromazine sulfoxide were qualitatively similar to those produced by chlorpromazine, although 2.5 to 5.0 times the dose was necessary to produce comparable effects (Fig. 18). In general chlorpromazine sulfoxide and chlorpromazine altered activating responses in a similar manner. Chlorpromazine sulfoxide elevated threshold and increased reactivity of the activating response (Fig. 20) and the increase in reactivity was greater than would have been predicted on the basis of increase in

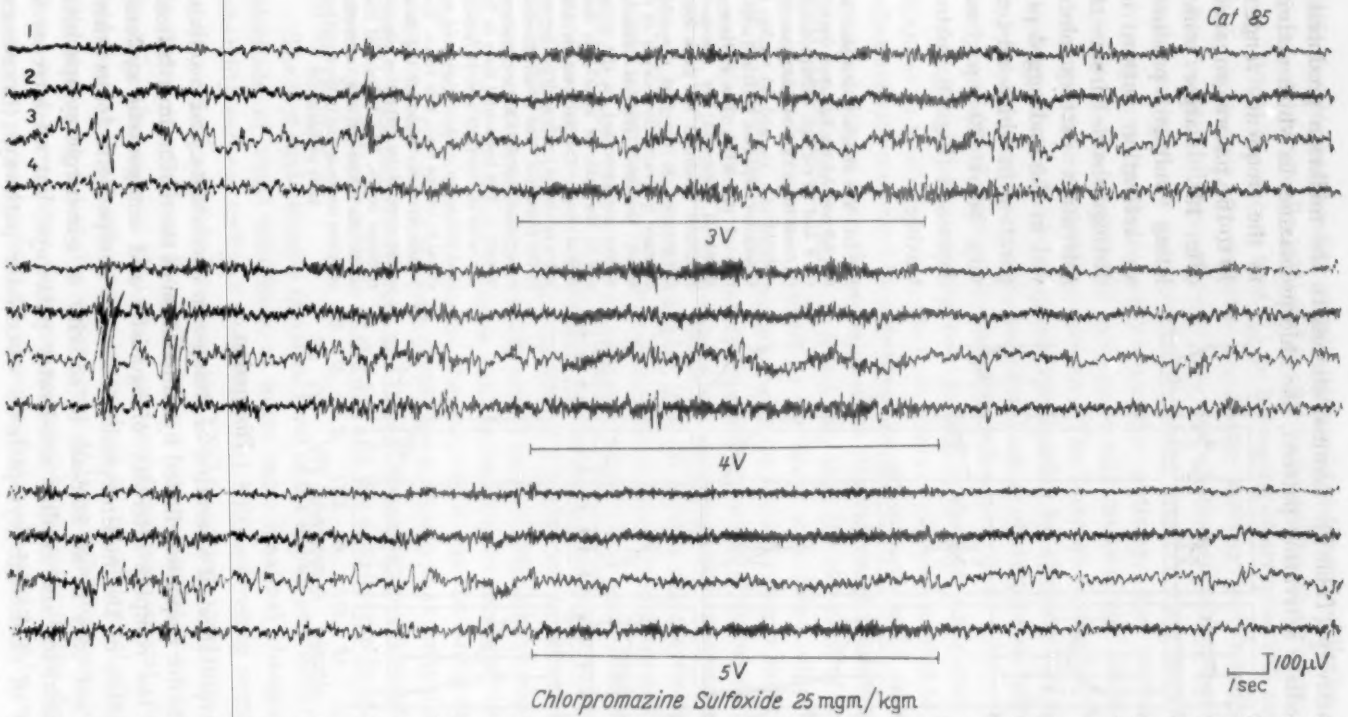

Fig. 19. The effect of chlorpromazine sulfoxide (25 mg/kg) on the EEG and its activation by increasing strengths of stimulation to the midbrain of a succinylcholine immobilized cat. Channels as designated in Fig. 6

delta activity (Table 2). Liminal stimuli to the midbrain produced a intermediate activation pattern, like chlorpromazine, in which activity in the frequency range of 10 to 16 c.p.s. was enhanced (Fig. 19). Larger stimulating voltage produced an activation pattern indistinguishable from the activation pattern observed in the undrugged preparation in which all activity below 20 c.p.s. was depressed (Fig. 19, bottom tracing).

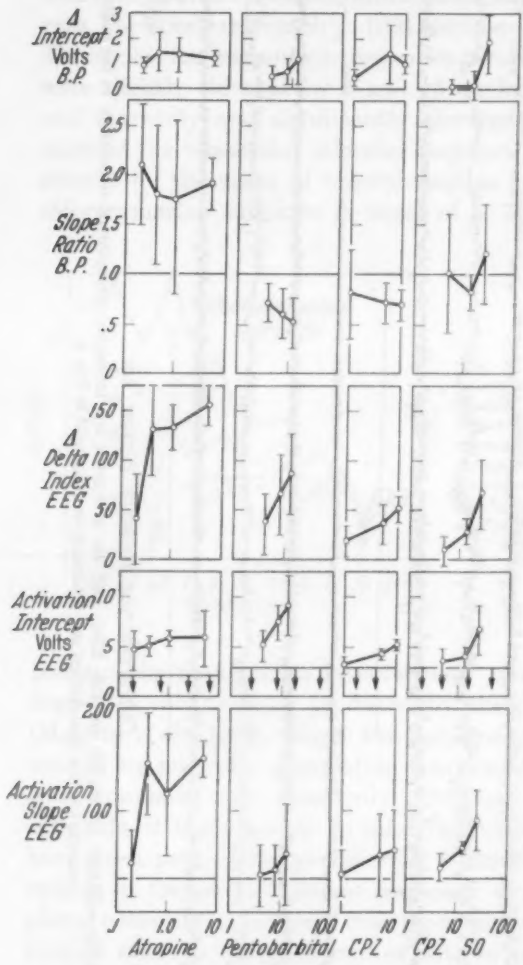

Fig. 20. The effects of atropine (0.2, 0.4, 1.0 and 5.0 mg/kg), pentobarbital (4, 8 and 12 mg/kg), chlorpromazine (1, 5 and 10mg/kg) and chlorpromazine sulfoxide (5, 15, and 25 mg/kg) on vasomotor responses, EEG and activation of the EEG. The increase in threshold (intercept) for vasomotor responses produced by these drugs are graphed in the first row while changes in reactivity (slope) of the blood pressure stimulus response curves are presented in the second row as the ratio of *slope after drug/control slope*. The increase in delta index produced by these drugs appears in the third row. The mean threshold for activation of the EEG are presented in row 4. The horizontal lines in this row with the vertical arrows indicate that the mean control threshold was equal to or less than this value. Row 5 illustrates the effect of the drugs on the slope of the activation stimulus response curve. The horizontal lines show the slope of the activation stimulus response line in the encéphale isolé preparation

Discussion

Interpretation of alteration of changes in excitability and reactivity of vasomotor responses elicited by stimulation of the midbrain is difficult due to the complex interplay of agonistic and antagonistic systems. Stimulation of the mesencephalon increases sympathetic tonus which results not only in an increase in activity of adrenergic sympathetic vasoconstrictor and cardiac accelerator pathways, but an increase in activity of cholinergic sympathetic vasodilator pathways (LINDGREN,

1955) and increases reflex vagally induced bradycardia. Reflex bradycardia was maximally inhibited by 0.2 to 0.4 mg/kg of atropine. LINDGREN (1955) has shown that 0.1 to 0.3 mg/kg of atropine will markedly block cholinergic sympathetic vasodilator activity peripherally. Both reflex vagal inhibition of heart rate and cholinergic sympathetic vasodilator activity are antagonistic to blood pressure rises produced by adrenergic sympathetic vasoconstrictor activity, and selective depression of the cholinergic systems would increase the reactivity of adrenergic vasoconstricting systems. The increase in reactivity of the blood pressure stimulus response relationship by atropine can therefore be partially attributed to the peripheral action of atropine on reflex vagal bradycardia and cholinergic vasodilator tone.

Atropine is known to depress conduction through autonomic ganglia (MARRAZZI, 1939), however, the dose levels of atropine needed to depress reflex activity mediated by autonomic ganglia (CAHEN and TVEDE, 1953) are much larger than those required to depress vagal inhibition of the heart (HENDERSON, 1923). It is unlikely that the elevation of threshold of vasomotor responses evoked by midbrain stimulation observed was due to depression of autonomic ganglia for the following reasons: (1) the small dose necessary to produce maximal elevation of threshold (0.4 mg/kg), (2) the elevation of threshold was not progressive as the dose levels were increased to 1 and 5 mg/kg, and (3) neither the reactivity of the stimulus response curve nor the maximal evoked blood pressure response was depressed by 5 mg/kg of atropine. Thus it has been concluded that atropine depresses centrally the vasomotor pathway descending from the mesencephalon. In this connection, it is relevant to note that DIRNHUBER and CULLUMBINE (1955) and VARAGIĆ (1955) have shown that several non-quarternary amine anti-cholinesterases produce blood pressure rises of central origin in the rat which can be antagonized by atropine. DALY and WRIGHT (1956) have shown that sarin (isopropyl methyl phosphorofluoridate) and TEPP (tetraethylpyrophosphate) increase sympathetic activity in the dog and the activity can be antagonized by atropine.

The fact that atropine in a dose level of 0.4 mg/kg produced complete blockade of vagal inhibition of heart rate, maximal changes in excitability and reactivity of vasomotor and EEG activating responses, as well as near maximal changes in the EEG frequency spectrum, suggests that atropine produces these effects by a common mode of action. These findings also suggest that there are peripheral and central cholinergic synapses that are effectively blocked to all physiological strengths of stimulation by 0.4 mg/kg of atropine. If these inferences are correct, it must be assumed that there are muscarinic synapses in the descending vasomotor pathways from the mesencephalon. It must also be postulated

that there are atropine insensitive synapses in parallel with the atropine sensitive synapses to account for vasomotor responses evoked by above threshold stimuli following 0.4 mg/kg or more of atropine. It appears that there are at least two pharmacological different pathways in the descending vasomotor system.

A similar pharmacological redundancy may be present in the ascending activating system. Although atropine produced a marked elevation in the threshold of the activation response which was maximal following 0.4 mg/kg, the reactivity of the activating response was greater with this dose level than with 0.2 mg/kg. Dibromopyruvic acid, an agent which mimics many of the peripheral muscarinic actions of acetylcholine (MARTIN *et al.*, 1958), and muscarine (RIEHL *et al.*, 1960) have been shown to activate the EEG and that this activation is blocked by atropine. The fact that *l*-hyoscyamine is more potent than *d*-hyoscyamine in producing EEG changes (BRADLEY and ELKES, 1957) and depressing EEG arousal response (DOMINO, 1959) lends additional support to the hypothesis that central muscarinic synapses are involved in the origin and regulation of cortical electrical activity. If a muscarinic synapse is present in the ascending pathway of the activating system and, for the reasons previously mentioned, it is assumed that muscarinic synapses are completely blocked by 0.4 mg/kg of atropine, it is necessary to postulate a parallel pathway which does not involve muscarinic synapses to explain activation observed in the presence of the larger doses of atropine.

Because the drugs studied produce different types of depression their potency cannot be compared in any strict sense. However, an estimate of relative effectiveness in depressing vasomotor responses evoked by midbrain stimulation will serve a purpose in comparing changes in vasomotor excitability with changes in excitability in the midbrain activating system. The range of doses necessary to produce a 1-volt rise in threshold of vasopressor responses are: atropine, 0.2—0.4 mg/kg; pentobarbital, 8—12 mg/kg; chlorpromazine, 5 to 10 mg/kg; and chlorpromazine sulfoxide, 15—25 mg/kg. The order of relative effectiveness is as follows: atropine is 20 to 60 times more potent than pentobarbital; pentobarbital is approximately equipotent to chlorpromazine; and chlorpromazine is 1.5 to 5 times as potent as chlorpromazine sulfoxide. A comparable estimate of the effectiveness of these drugs in depressing excitability of the activating system was obtained by determining the dose necessary to produce an approximately 2.5-volt elevation of threshold. Thus 0.2 mg/kg of atropine, 4 mg/kg of pentobarbital, 10 mg/kg of chlorpromazine, and between 15 and 25 mg/kg of chlorpromazine sulfoxide were approximately equally effective. The order of relative effectiveness is: atropine is 20 times as effective as pentobarbital, pentobarbital is twice as effective

as chlorpromazine, and chlorpromazine is 1.5 to 2.5 times as effective as chlorpromazine sulfoxide.

Pentobarbital, using depression of vasomotor excitability as a base, was the most effective agent in depressing excitability of the activating response. The frequency spectrum produced by pentobarbital was very similar to the frequency spectrum of the cerveau isolé preparation. These findings seem to support the view that pentobarbital selectively depresses the activating system (ARDUINI and ARDUINI, 1954; FRENCH *et al.*, 1953; and KING, 1956). However, this interpretation must be qualified for, although pentobarbital markedly depressed the inhibitory action of midbrain stimulation on delta activity, the ability of midbrain stimulation to accelerate alpha activity was enhanced and exaggerated. Frequency acceleration produced by midbrain stimulation following pentobarbital was graded and dependent on strength of stimulation. The more intense activating responses evoked in the presence of pentobarbital markedly resembled the high voltage activity with a frequency range of 21 to 32 c.p.s. described by BRAZIER (1945, 1948) for barbiturates. Because a continuum, ranging from activity in the range of 4 to 14 c.p.s. to a range of 22 to 30 c.p.s., could be produced by increasing stimulus strength to the midbrain it is suggested that the high voltage high frequency activity commonly produced by barbiturates is, in a sense, activated or accelerated barbiturate spindle activity.

The activating response observed after atropine was predominantly one of decreased activity at all frequencies below 22 c.p.s. with little or no tendency of enhancing and accelerating various frequencies of activity. Thus the activating system seems to have two distinct actions on cortical activity that are most clearly differentiated when activation in the presence of atropine is compared to activation in the presence of pentobarbital: (1) a depression or inhibition of cortical waves, and (2) an acceleration of the frequencies of brain waves.

The ability of the EEG activating system to inhibit and abolish a wide variety of cortical activity has been shown by many investigators (MORUZZI and MAGOUN, 1949; WHITLOCK *et al.*, 1959; and PURPURA, 1956). It may be that "deactivation" observed by DOMINO (1955) represents the predominance of the inhibitory effect of the activating response. It is frequently difficult to decide whether inhibition of certain activity is only apparent in that it may represent driving of the activity at a higher frequency or whether the waves are depressed in amplitude. In some preparations (encéphale isolé and occasionally in the succinylcholine immobilized cat) increase in the frequency of activity in the delta-theta range and in the alpha range was clearly demonstrated during liminal midbrain stimulation. However, in animals receiving atropine, though distinct bursts of spindle activity in the alpha range were common,

stimulation of the midbrain never produced discernible acceleration of an alpha peak as was commonly observed after pentobarbital. It may be that the spindles produced by pentobarbital arise from a different neuronal substrate than those produced by atropine. Thus it would seem that either the midbrain reticular system has two distinct types of action (e.g., inhibitory and facilitatory), or it affects different neuronal substrates which are responsible for particular brain waves in different ways.

Chlorpromazine and chlorpromazine sulfoxide produce similar EEG changes. Their frequency spectra were similar and bore certain resemblances to the frequency spectra of the encéphale isolé preparation and the atropine treated succinylcholine immobilized preparation. It is unlikely, however, that chlorpromazine and chlorpromazine sulfoxide produce their EEG effects by the same mechanism as atropine since they had no observable vagolytic effect in the doses employed. The similarity between the EEG changes produced by chlorpromazine and chlorpromazine sulfoxide and the EEG of the encéphale isolé preparation may bear on the hypothesis advanced by BRADLEY (1958) that chlorpromazine acts by depressing afferent inflow to the activating system. The similarity of the frequency spectrum of the chlorpromazine treated succinylcholine immobilized cat to the frequency spectrum of the encéphale isolé preparation suggests that chlorpromazine may depress sensory inflow to the activating system. DE MAAR *et al.* (1958) and KILLAM and KILLAM (1958) have found that single reticular potentials evoked by peripheral nerve stimulation are enhanced by chlorpromazine, however, the recovery cycle of the evoked potentials is prolonged (DE MAAR *et al.*, 1958). Consequently if there is an inhibition of sensory input to the activating system by chlorpromazine, this depression would seem to be on the maximal number of impulses the activating system can accept in a given period of time.

Though it is possible to explain the decreased excitability of vasomotor responses and EEG activating responses elicited by midbrain stimulation following chlorpromazine by assuming there is a decrease in facilitatory tone to these systems resulting from diminished sensory input, it seems equally probable that the decrease in the excitability produced by chlorpromazine and chlorpromazine sulfoxide results from a direct depressant action on these systems.

The mode of action by which chlorpromazine produces its depressant effect on the excitability of the activating system has been related to its adrenergic blocking property (BONVALLET *et al.*, 1954; BRADLEY and HANCE, 1957). Chlorpromazine is both an adrenergic blocking agent and an adrenergic potentiator (MARTIN *et al.*, 1960) while chlorpromazine sulfoxide is predominantly an adrenergic potentiator (MORAN and BUT-

LER, 1956; MARTIN *et al.*, 1960). Doses of chlorpromazine (5—10 mg/kg) and chlorpromazine sulfoxide (15—25 mg/kg) that produce comparable depression of vasopressor responses and activating responses do not produce comparable degrees of adrenergic blockade. Chlorpromazine in doses of 5 and 10 mg/kg depresses *l*-epinephrine pressor responses while prolonging levarterenol pressor responses; chlorpromazine sulfoxide (20 mg/kg) does not depress but prolongs *l*-epinephrine pressor responses, and both enhances and prolongs levarterenol pressor responses (MARTIN *et al.*, 1960). Thus depression of vasomotor and activating responses evoked by midbrain stimulation by chlorpromazine and chlorpromazine sulfoxide appears to be better correlated with the adrenergic potentiating action of these drugs than with their adrenergic blocking property. Atropine, chlorpromazine and chlorpromazine sulfoxide increased both threshold and reactivity of the activating response. Comparison of the reactivity of the activating response in the encéphale isolé preparation to the reactivity following atropine, chlorpromazine and chlorpromazine sulfoxide indicated that the increase in reactivity following these agents was not solely a consequence of the increased slow wave activity. No explanation of the divergent effects of these agents on excitability and reactivity is offered; however, the functional significance of such a dissociation may be that at low levels of stimulation responsivity is depressed by these agents while at higher levels of stimulation responsivity may be unattenuated or exaggerated.

Summary

A method for the quantification of the effects of drugs upon the EEG and the EEG activating response using an Offner frequency analyser has been presented. The activating response has been shown to be graded in three respects: (1) latency of onset, (2) degree of depression of certain brain waves, and (3) degree of acceleration of frequency of certain brain waves. Using the degree of depression of activity of brain waves in the frequency range of 1.5 to 3.5 c.p.s. by graded stimuli to the midbrain reticular formation, it was possible to obtain estimates of the effect of drugs on the excitability and reactivity of the activating response. Simultaneous estimates of the excitability and reactivity of vasopressor responses to midbrain stimulation were obtained.

Both the ascending activating system and descending vasomotor system seem to involve a muscarinic (atropine sensitive) synapse, however, evidence has been presented that, in addition to pathways involving a muscarinic synapse, these functions can be mediated over pathways devoid of muscarinic synapses.

Comparing activation patterns obtained in the presence of atropine with those obtained in the presence of pentobarbital, it has been possible

to dissociate two effects of activation on spontaneous cortical potentials: (1) inhibition or depression of cortical waves, and (2) acceleration of frequency of cortical waves. Both of these effects appear to be graded. Evidence has been presented indicating that the high voltage fast activity observed after small to moderate doses of barbiturates may represent spindle activity that has been accelerated by the activating system.

Chlorpromazine and chlorpromazine sulfoxide were found to decrease the excitability of both the ascending activating system and the descending vasomotor system. The depression of excitability was better correlated with the adrenergic potentating property of these agents than with their adrenergic blocking activity.

Atropine, chlorpromazine and chlorpromazine sulfoxide were found to increase both threshold and reactivity of the ascending activating system.

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Withdrawal Reactions from Meprobamate, Alone and Combined with Promazine: A Controlled Study

By

Leo E. Hollister and Frederick S. Glazener

With 1 Figure in the Text

(Received February 5, 1960)

Early clinical investigators recognized a withdrawal syndrome from meprobamate (Lemere 1956b, Barsa and Kline 1956; Hollister et al. 1957). Reactions were reported when patients were deprived of the drug while taking from 4.8 to 20 gm. daily. The usual syndrome was characterized by insomnia, restlessness, agitation, tremors, gastrointestinal symptoms and, in some cases, by newly-appearing seizures or psychotic reaction. Severity appeared dependent upon dosage, duration of treatment, rate of discontinuance and the personality structure of individual patients. Those with previous histories of addiction to alcohol, barbiturates or narcotics were especially prone to withdrawal effects (Mohr and Mead 1958; Lemere 1956a).

Method of Study

This study had three parts: To test withdrawal from meprobamate 1. in patients treated with usual therapeutic doses, 2. in patients receiving large doses, and 3. in patients receiving large doses of meprobamate-promazine combination. In each instance, withdrawal was accomplished by substituting placebos of identical appearance without the patient's knowledge.

Sixty patients treated with therapeutic doses (0.4 to 4.8 gm. daily, 20 over 1.6 gm. daily) for 3 weeks to 12 months (median 4 months) were switched to placebos by substituting the ward supply of drug without telling ward personnel. After 7 days, a new supply of active medication was furnished. Psychiatric diagnoses of these patients were schizophrenic reactions in 26, chronic brain syndromes in 18, psychoneuroses in 10, affective disorders in 5 and personality disorder in 1. All but 8 were men, ranging from 24 to 73 years in age. On the 4th day after a ward's supply of drug had been switched, patients and personnel on that ward were questioned about unusual symptoms or signs in the patients concerned, and the nursing notes on each patient were carefully reviewed. From these sources, changes in patients' symptoms,

signs or behavior as the result of abruptly withdrawing meprobamate were recorded.

Twenty-one patients treated chronically with large doses of meprobamate (3.2 to 8 gm. daily) were carefully observed on a medical ward during the withdrawal period. Placebos were substituted for 7 days without the knowledge of the patient but with that of ward personnel. Treatment with meprobamate had been continuous for from 2 weeks to 13 months (median 4 months), the maximum dose having been given for from 1 to 4 weeks prior to withdrawal. All the patients were men, ranging in age from 35 to 70 years. Psychiatric diagnoses were schizophrenic reaction in 12, psychoneurosis in 3, chronic brain syndrome in 3 and affective disorder in 2. Before switching to placebos, blood was drawn for determination of plasma meprobamate levels (WALKENSTEIN et al. 1958), and an electroencephalogram was obtained. At 24, 48, 72 and 96 hours after discontinuation of meprobamate, these procedures were repeated as possible. Careful clinical observations of these patients were made during the week following drug withdrawal. Longterm behavior patterns of patients selected for these studies were known to ward personnel prior to their receiving meprobamate. Thus, changes during the withdrawal period could be distinguished from recrudescent symptoms or spontaneous fluctuations in clinical course.

Ten patients treated chronically with capsules of a combination of meprobamate 200 mg. and promazine 25 mg. were withdrawn from the drug under similar conditions. These patients were receiving from 4.8 to 6.4 gm. of meprobamate and 600 to 800 mg. of promazine daily at the time of withdrawal. These dose levels had been attained by progressive increments over several weeks time. Four of these patients had been previously withdrawn from meprobamate in comparable doses. In addition to determinations of plasma meprobamate levels and electroencephalograms, daily urine specimens were obtained for qualitative determination of promazine (FORREST and FORREST 1957).

Results

Only 10 patients of 60 removed from meprobamate while taking customary therapeutic doses had symptoms from drug withdrawal. Insomnia, psychomotor agitation, tremors, emotional lability and gastrointestinal disturbances were observed, but none of the reactions was severe or prolonged. In some patients, these symptoms were analogous to those for which the patients had originally been treated. Four patients on one ward stated they had been receiving "dummies", two of them reporting recrudescent symptoms. Oddly, they timed the switch to placebos as having occurred a week or more earlier, rather than in the preceeding 4 days.

Sixteen of 21 patients abruptly withdrawn from large doses of meprobamate had a syndrome of increased psychomotor activity, tremors, insomnia, emotional lability and gastrointestinal disturbances (loss of appetite, nausea, or vomiting) lasting for several days and then subsiding. The symptoms in these patients were considerably more severe

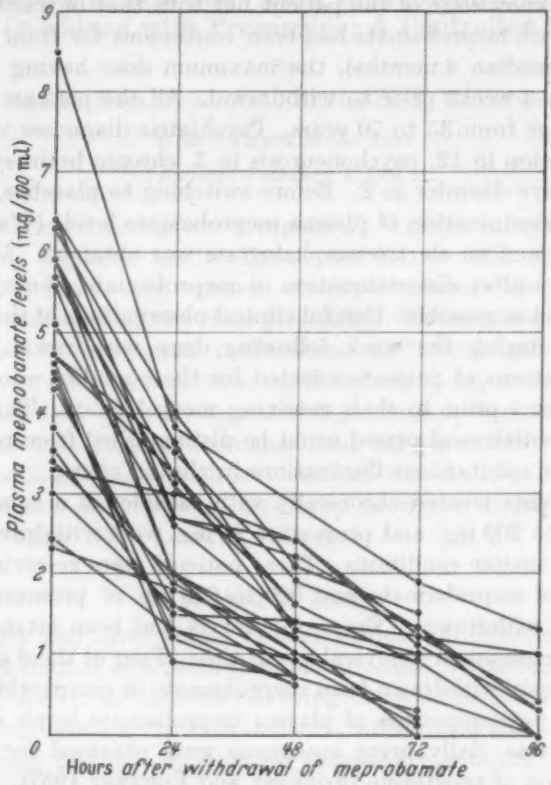

Fig. 1. Plasma meprobamate levels after abrupt withdrawal of chronically administered drug (23 Patients)

than in patients on ordinary doses, sometimes making clinical or laboratory measures difficult or impossible. Symptoms appeared as early as within the first 24 hours and as late as 96 hours after drug withdrawal. Neither the time of appearance nor the severity of symptoms could be correlated with changes in plasma levels of meprobamate which varied from 2.3 to 6.3 mg. per 100 ml. at the time of withdrawal on daily doses of 3.2 to 8.0 gm. (mean 5.8 gm.). None of the patients in this group had any seizures. Electroencephalograms were abnormal in 14 of 19 patients just prior to withdrawal while high doses of meprobamate were being given, fast (20/s) activity being most common. Subsequent tracings

tended toward normal or the development of abnormal slowing (6—8/s), the latter appearing 48 hours after discontinuation of drug.

Combining meprobamate and promazine did not appreciably change the frequency or course of withdrawal reactions from large doses. A withdrawal syndrome comparable to that described above was experienced by 8 of 10 patients in whom the combined medication was discontinued. Four patients previously withdrawn from large doses of meprobamate alone had comparable reactions, except for one who had 2 convulsions 72 hours after stopping the combined drugs. Four of 6 patients being withdrawn from the combined drugs had normal electroencephalographic tracings. Two patients had abnormal patterns with mixed fast (20/s) and slow (5/s) activity. Tracings were not obtained on the patient who developed seizures because his behavioral symptoms prevented adequate cooperation. Plasma levels of meprobamate varied in this group from 3.4 to 8.5 mg. per 100 ml. at the time of withdrawal on daily doses of 4.8 to 6.4 gm. (mean 5.6 gm.). As before, clinical symptomatology could not be correlated with changes in plasma levels. Promazine in the urine could be detected by the qualitative test for from 3 to 6 days following drug withdrawal, but most had disappeared by the 4th day.

The rate of disappearance of meprobamate from the blood in patients chronically treated deserves special mention. Measures were obtained in 23 patients treated with large doses of meprobamate alone (16 patients) and the meprobamate-promazine combination (7 patients). The trends are shown in graphic form in Fig. 1. At 24 hours after discontinuation, the median proportion remaining was 50 percent (range 20—90%); at 48 hours, 28 percent (range 11—73%); at 72 hours, 14 percent (range 0—33%); at 96 hours, 8 percent (range 0—14%). Despite the wide variability between patients, the drug had a plasma half-life of roughly 24 hours.

Discussion

Withdrawal of meprobamate at ordinary doses produced few effects. An earlier study of 60 patients switched to placebos while taking 1.2 gm. daily produced mild symptoms in only 2 patients (Boyd et al. 1958). The higher doses used in the present study probably accounts for the increased frequency of symptoms encountered.

The frequency and intensity of withdrawal reactions increased with higher doses of meprobamate. A study of prisoners receiving 3.2 to 6.4 gm. daily revealed withdrawal symptoms or signs in 42 of 49 subjects, with an unstable electroencephalogram in 38 (Stough 1958). Two patients experienced seizures, one at 16 hours, the other at 44 hours following withdrawal. Forty-four of a group of 47 mental hospital patients treated with 3.2 or 6.4 gm. daily doses experienced an abstinence

syndrome, 3 developing seizures and 8 hallucinosis (HAIZLIP and EWING 1958). Severe reactions were significantly more frequent at the higher dose level. Each of 12 psychiatric patients treated with an average daily dose of 10 gm. for 4 weeks had withdrawal reactions, 2 with generalized seizures and 3 with acute psychotic reactions (SHAGASS et al. 1959). Fast activity similar to that from barbiturates appeared in the electroencephalograms of these patients while peak doses were being given. We were unable to reach the 10 gm. dose level in our patients because of severe ataxia and incoordination. In other respects, our patients experienced similar effects.

Reactions to withdrawal of meprobamate combined with promazine have neither been reported nor previously studied. Our hypothesis was that promazine might protect against reactions as phenothiazine derivatives are more cumulative. This guess proved to be entirely wrong, both the frequency and severity of withdrawal reactions from the combined drugs being comparable to that frommeprobamate alone. As judged by the qualitative urine test, excretion of promazine was only slightly slower than meprobamate. Electroencephalographic changes were less frequent with the combination. Possibly the effects of promazine cancelled those of meprobamate, as chronic administration of phenothiazine derivatives tends to produce slowing contrasted with the fast activity from meprobamate (HOLLISTER and BARTHEL 1959). Both patients with abnormal tracings had mixtures of each abnormality.

After chronic administration, the half-life of meprobamate is approximately 24 hours. With sharpest declines in plasma levels in the first 48 hours, it is logical that most withdrawal reactions should appear in that period. Our only patient with seizures had an unusually rapid decline in plasma levels, only trace amounts being detected when seizures appeared at 72 hours. Disappearance of meprobamate from plasma appears to be even more rapid following acute doses, suggesting that survival for 48 hours after a suicidal dose favors recovery.

Summary

Only 10 of 60 patients on meprobamate experienced mild withdrawal symptoms when switched from customary doses (0.4 to 4.8 gm. daily, median 1.6 gm.) to placebos in a blind study. With daily doses of 3.2 to 8 gm. (mean 5.8 gm.), placebos produced a definite withdrawal syndrome in 16 of 21 patients. Increased psychomotor activity, tremors, insomnia, emotional lability, and gastrointestinal disturbances appeared from 24 to 96 hours after withdrawal of active drug. Electroencephalograms were abnormal in 14 of 19 patients tested, tending toward normal subsequently. None of the patients had seizures. A similar syndrome was observed in 8 of 10 patients withdrawn from a combination of

meprobamate (4.8 to 6.4 gm. daily, mean 5.6 gm.) and promazine (600 to 800 mg. daily). One patient had seizures 72 hours after discontinuation of the drugs.

Plasma levels of meprobamate varied between 2.3 and 8.5 mg. per 100 ml. at the time of withdrawal. Measures of daily plasma levels in 23 patients indicated a half-life of approximately 24 hours for the drug, with wide individual variations.

Withdrawal reactions from large doses of meprobamate were frequent, though not related to initial plasma levels or electroencephalographic changes. Reactions similar in frequency and intensity were noted when promazine was combined with meprobamate. Symptoms from withdrawal at ordinary therapeutic doses were infrequent and mild, resembling recrudescence of symptoms being treated.

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Short Communications · Kurze Originalmitteilungen
Communications brèves

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A Use of Motion Pictures in Double Blind Technique

By
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(Received October 21, 1959)

Since man first attempted to make medicine more science than art, he has been plagued by a seemingly impossible problem. How can a man objectively evaluate his fellow man? Many methods have been suggested, but all too often researches still must simply look at a patient and decide whether or not a new drug has helped. Here we offer a new method which at least submits subjective opinions to a statistical analysis.

Matthews, in a recent publication reviewing his experimental use of thiopropazate ("Dartal", a new tranquilizing drug released by G. D. Searle and Co.), stated that pre- and post-treatment motion pictures of nine patients demonstrated that the drug had a marked suppressor effect on the choreoform movements of Huntington's Chorea. Plans were made immediately to repeat this experiment at our hospital[1].

Our technique was without specific plan since none of us were experienced in this type of research. We assembled five patients, and photographed them individually while they removed some outer garment. We then administered the experimental drug (thiopropazate, 20 mg. t. i. d.) for a period of eight weeks, reassembled our patients and rephotographed them, repeating as nearly as possible the initial technique.

When the films were reviewed by the experimentors, improvement was not clearly demonstrated. We became immediately aware that further simple review of the films by other observers would only compound our own dissension: those doctors optimistic about recent drug discoveries would see improvement while the pessimistic observers would see none.

The Technique

Before calling in other observers to view the film strips the following schema was devised.

The before and after film strips of each individual patient were spliced together, but in random sequence. Three film-strips were in

[1] D. Dix Hospital, Raleigh, N. C.

before-after sequence, and two in after-before sequence. Again the choice of patient for each sequence was randomly chosen.

Since well-trained personnel tend to have prejudices about new drugs purported to treat previously untreatable diseases, three people were chosen as a group to view the movies. They were a board-eligible psychiatrist, a psychiatric resident, and a relatively or totally inexperienced person (office personnel or student nurse). Five such groups were selected. The series of five films was then shown to each group. In all of the five showings the individual films appeared in the same before-after sequence. However, the five groups of observers saw the five patient films in five different orders; i. e., Group I saw the films in a series of A, B, C, D, E; Group II saw them in a series of B, C, D, E, A, etc. This revolving order of presentation was used to compensate for any learning by the observers, or for any artifact in the photographic technique which would have provided clues for easier identification of subsequent films. Prior to each film showing, the group was instructed to state on a simple scoring sheet the before-after sequence of each of the five strips. They were also instructed about the nature of the choreoform movements which were purported to be suppressed by the drug. The strips were then shown from separate reels allowing the observers to score their opinions of each patient immediately. The senior staff observers routinely complained that the experiment was invalid because the films were not long enough, that the patients were not doing exactly the same thing, and that they could see no difference at all in some patients. The lay participants stated only that they enjoyed participating. They had no other comments.

Statistics

The results were then collected and evaluated. There were a total of 75 possible right answers, 25 each for the psychiatrists, the residents, and the laymen. The psychiatrists correctly scored 18/25, the residents 16/25, and the laymen 15/25.

The probability of obtaining 49 or more correct guesses out of 75 attempts, if in fact there was a 50—50 chance of being correct on any given guess, is $P = 0{,}006$. Hence it is clearly demonstrated that the group of 15 observers were discriminating between the before-after film sequences (and by implication the drug effect). There were not enough guesses (25) in each of the 3 groups to detect statistically significant differences among them. However, there is some indication that if a larger number of guesses were made by each of the above 3 groups, the proportion of correct guesses for the senior psychiatrists would have been significantly greater than the proportion of correct guesses in either of the other two groups.

If the following table is constructed a test of *homogeneity* can be performed. That is we can test the hypothesis that the probability of a patient's film sequence being guessed correctly by an observer is the same from patient to patient. The appropriate Chi-Squared statistic for testing this hypothesis yields the value $X^2 = 7.89$. Since the 5% critical value for X^2 having 4 degrees of freedom is 9.49 the hypothesis is not rejected. We can couclude, therefore, that the evidenced discriminating ability of the fifteen observers cannot be statistically ascribed to exceptional detection of any specific patients.

Table

Patient	Was Guessed Correctly	Was Not Guessed Correctly	Total
A	9	6	15
B	7	8	15
C	9	6	15
D	14	1	15
E	10	5	15
	49	26	75

Discussion

With this experimental technique we have statistically judged a subtle human response to a drug. Direct observation of the patient on the ward would have been impossible. Since each of the five patients was on a separate ward, each direct observation would have been completely subjective and further invalidated by the tendency of the symptoms to increase as anxiety increases. Simple observation of the films by the experimentors would have been almost as subjective. Majority and minority reports would have been necessary which, likely, would have reported only the pre-existing prejudices of each experimentor.

A review of the movies by an unstructured larger group would have compounded the dissensions of the group of experimentors.

By having the films reviewed by three classes of professional personnel, we were able to further qualify the data since one would predict that personnel more familiar with the symptoms of the disease would be more able to detect slight variations in these symptoms. We were also able to demonstrate that our belief that the patients did improve was not biased by dramatic improvement in any one patient.

We suggest that this technique may be applicable to other research projects which heretofore have defied an objective examination by many observers. For instance, the same technique might be utilized with before and after tape recordings, in evaluations of psychotherapy.

Summary

In an effort to subject minimal drug results to objective and statistical evaluation we have used a new technique utilizing motion pictures. Our patients were photographed, given a drug (thiopropazate) for eight

weeks, and then rephotographed. The films were spliced in random before and after sequences. Five juries each consisting of a trained psychiatrist, a psychiatrist in training, and a layman were then asked to judge the strips as to whether the film had been exposed before or after the administration of the drug. The results obtained were then subjected to statistical evaluation demonstrating by inference that the drug effect was notable. This drug effect had not been notabe on subjective evaluation. We submit this, a new technique for double blind studies.

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Comparison of Excited Phases after Sedatives and Tranquilizers

By

GEORGE W. READ, WINDSOR CUTTING and ARTHUR FURST

With 6 Figures in the Text

(Received December 3, 1959)

The transitory excitement after barbiturates has been noted in the clinic and the laboratory for many years although it appears to have had little detailed study. By contrast, an excited phase has not been characteristic after chlorpromazine. To see how general this difference was between sedatives and tranquilizers, the initial courses after the administration of a number of drugs, including barbiturates, alcohol and chlorpromazine have been compared. Gross activity in mice, as recorded on an activity table, was taken as a simple measure for the comparison.

Methods

Animals and equipment. Mice of the Swiss-Webster strain with an average weight of 23 g and of either sex were tested individually on an activity table. This apparatus consisted of a light plastic container supported on a spring lever; movements closed a microswitch which activated an electrical counter (CUTTING *et al.* 1959). The animals could move freely in the container which was cylindrical, 12 cm in diameter and 12 cm high.

Procedure. A typical run followed several steps:

a) A mouse was weighed, injected subcutaneously with 0,1 ml saline, and then placed on the activity table.

b) After 4—5 min for familiarization, movements were counted for three five-minute periods, the average representing the control count.

c) As soon as the third five-minute control period was completed the mouse was injected with the test drug, replaced on the table, and counting begun immediately. Counting was continued, in five-minute periods, over a one and one-half hour period.

d) Five mice were run at each dose level; a group of ten mice re-injected with saline furnished normal curves.

Recording. For ease of comparison, all results with each mouse were expressed as a percentage of the average during the control periods. Thus, if the control average was 50, that and all other counts would be multiplied by two; conversely, if the control was 200, then all the counts

were divided by two. The adjusted values for the five mice of each group were then averaged, graphed on semi-log paper and a smooth curve drawn, as in Fig. 1. The average deviation of all points from the smoothed curves of ten control mice was ± 39. Values for the ten individual curves were: ± 52, 54, 15, 170, 32, 7, 15, 14, 11, 20.

Administration of drugs. Phenobarbital, chlorpromazine, hydroxyzine, pipradrol and ethanol were given subcutaneously in saline solution; buclizine, reserpine and meprobamate were given similarly but in suspension. Doses were chosen which would produce obvious, but not maximal, effects.

Results

Drugs with stimulant phases. In Fig. 2 the activity curve of phenobarbital (120 mg/kg) shows a marked initial stimulatory phase during

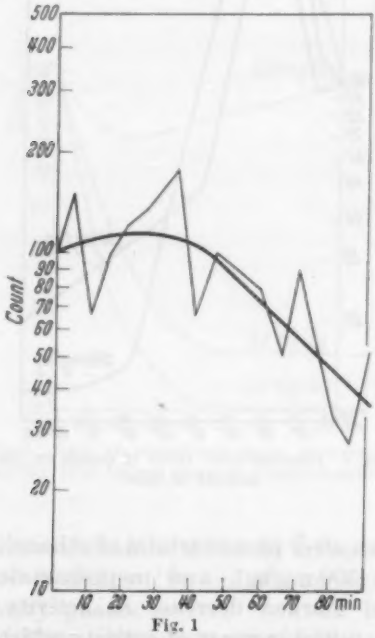

Fig. 1

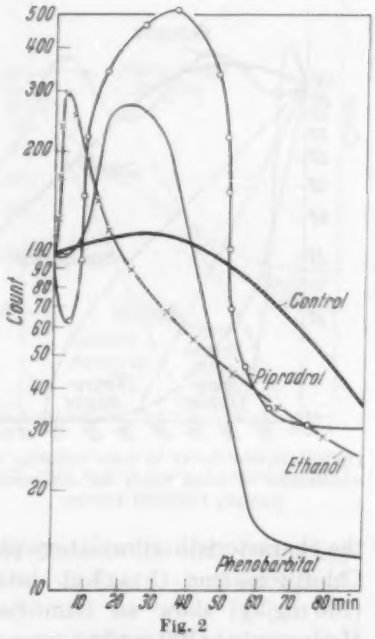

Fig. 2

Fig. 1. Activity of control mice on the activity table; average counts (per 5 min) for 10 animals, showing the averages of the values observed, and the derived smooth curve. There is an early slight increase in activity, and then a gradual decrease over the course of an hour and a half, interpreted as representing initial exploration and then subsequent relaxation and napping

Fig. 2. Activity curves of mice following administration of drugs which produced an initial period of increased activity

the first one half hour and the full development of depression by one hour. In the same figure, the initial part of the curve for ethanol (5 ml/kg) resembles that for phenobarbital except for a more rapid onset. For

comparison, the curve for the stimulant agent, pipradrol (80 mg/kg) is shown. Except for greater magnitude, the stimulatory part of the curve is not unlike that with phenobarbital.

Thus, the initial phases of phenobarbital and ethanol are seen to be characterized by increased activity in the mouse; the increased activity resembles that produced by pipradrol, a stimulant.

Drugs without stimulant phases. In Fig. 3 the activity curves of chlorpromazine and several other tranquilizers are shown, none exhibiting

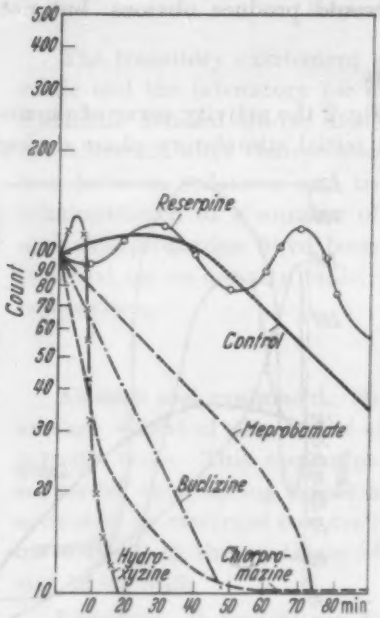

Fig. 3. Activity curves of mice following administration of drugs which did not produce initially increased activity

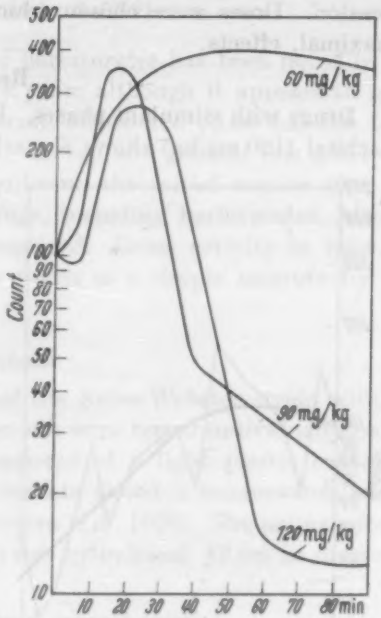

Fig. 4. Phenobarbital: effect of dosage on the activity of mice

the characteristic stimulatory phase seen after phenobarbital or ethanol. Chlorpromazine (1 mg/kg), buclizine (300 mg/kg), and meprobamate (100 mg/kg) show an immediate and marked decrease in activity. Hydroxyzine (100 mg/kg) gives a brief, initial increase of activity which may have been an artifact as the animals bit and scratched at the site of injection for some minutes. Reserpine shows little difference from the control in one and one-half hours of observation, as might be expected from its normally slow onset of effect (WOODSON *et al.* 1957).

Thus, it is clearly shown that the characteristic period of excitation following the sedative, phenobarbital, is not seen following several drugs of the tranquilizer group.

Effect of dosage on stimulatory phase. A comparison of three different dosages of phenobarbital (60, 90 and 120 mg/kg) on activity are shown in Fig. 4. In each case there is the expected initial increase in activity, and to approximately the same degree. With the smallest dose the excitatory phase lasted throughout the period of observation without any appearance of sedation.

The effects of three different dosages of chlorpromazine (0,25, 0,5, and 1 mg/kg) are shown in Fig. 5. In no case is there a stimulatory

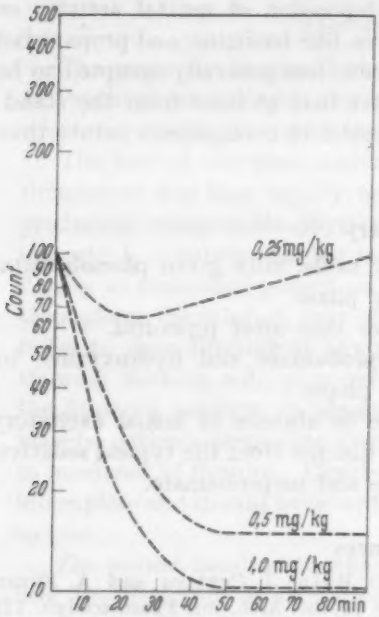

Fig. 5. Lack of stimulatory phase in mouse activity after various doses of chlorpromazine

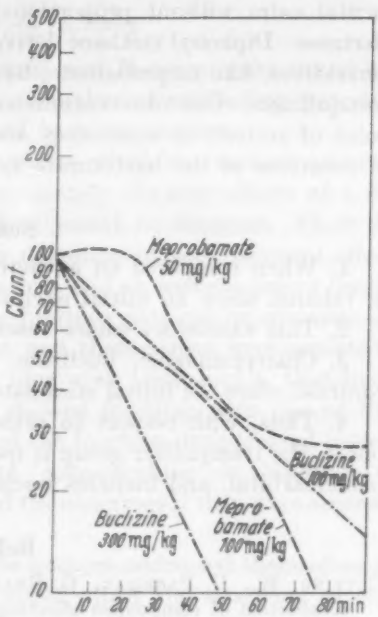

Fig. 6. Lack of stimulatory phases in mouse activity after various doses of meprobamate or buclizine

phase. Likewise, different dosages of meprobamate (50 and 100 mg/kg) and buclizine (100 and 300 mg/kg), as shown in Fig. 6, show no stimulatory phases.

Thus, although dosage varies the intensity of the sedative or tranquilizing response, it does not greatly alter the initial phase, either qualitatively or quantitatively.

Discussion

The phase of excitation after barbiturates appears not to have been extensively studied. QUIGLEY in 1934 stated that in dogs "Excitation from barbital and phenobarbital was more frequent after small than with moderate dosages but the maximal dose of amytal produced marked

restlessness". Our results in mice show little difference in the height of excitation after different doses of phenobarbital but show a prolongation with minimal doses.

The presence of the excitatory phase after phenobarbital and ethanol, and its absence after chlorpromazine and other tranquilizers, is striking. The differentiation of tranquilizers from sedatives has posed some uncertainties. Chlorpromazine and reserpine have been generally accepted as typical tranquilizers, i.e. agents carrying the implication of mental calm without proportionate depression of mental activity or alertness. Diphenyl methane derivatives, like buclizine, and propanediol derivatives, like meprobamate, have been less generally accepted to be tranquilizers. Our observations suggest that at least from the standpoint of activity in mice, they are typical of tranquilizers rather than of sedatives of the barbiturate type.

Summary

1. When compared on an activity table, mice given phenobarbital or ethanol show an initial excitatory phase.

2. This excitatory phase resembles that after pipradrol.

3. Chlorpromazine, buclizine, meprobamate and hydroxyzine, by contrast, show no initial stimulatory phase.

4. Thus, with respect to presence or absence of initial excitatory phase, the tranquilizer group is quite distinct from the typical sedative, phenobarbital, and includes buclizine and meprobamate.

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Letters to the Editor · Briefe an die Herausgeber · Lettres à l'éditeur

Note to the Paper "The Influence of Side-Effects on the Reporting of Symptoms" by F. J. J. Letemendia and A. D. Harris

By

L. Lasagna

(Received April 15, 1960)

The paper by Doctors Letemendia and Harris in the initial issue of Psychopharmacologia[1] contains a number of misleading statements which may be further misinterpreted by many readers.

The first of the three major points to which the authors addressed themselves was how rapidly and accurately the side effects of a drug producing recognizable physical signs would be detected. Their data indicate 1. a substantial lag in the detection of such physical effects; 2. only an occasional patient on nicotinic acid showed consistent flushing throughout the trial; 3. four of the fourteen patients on nicotinic acid failed to show flushing at any time, and three others were reported as showing flushing only once over a nine-week trial; and 4. that five of the fourteen patients on placebos showed flushing, with one of these placebo patients surpassing eleven of the fourteen drug-treated patients in incidence of flushing. Clearly, the "code-breaking" in this study was incomplete and should have confused the observers if they were amenable to bias.

The second question to which the authors addressed themselves was how the detection of side effects would affect the reporting of other symptoms. The data here indicate that other "somatic symptoms" were reported equally frequently in the drug-treated and placebo-treated groups, and that such symptoms were noticed with especial frequency in the patients who demonstrated flushing. The authors interpret the latter fact as indicating that "one effect of drugs which produce somatic side effects is to cause increased attention to be paid to those patients who show changes". An alternative explanation is that those patients who demonstrate flushing are the patients most likely to report other side effects. This latter explanation, in contrast to that of Letemendia and Harris, would imply that the reporting of these symptoms is more "patient-derived" than "observer-derived".

The third question to which the authors addressed themselves was whether the detection of side effects would lead to differences in the assessment of mental state. The answer was no.

[1] Letemendia, F. J. J., and A. D. Harris: Psychopharmacologia 1, 39—47 (1959).

The authors then go on to make the point that only if guesses as to which patients are receiving active medication are made at random (i.e., not more or less correct than expected by chance) is the double blind technique valid. The authors state that if the observers guess correctly in every case "the double blind procedure is then useless and provides no safeguard against the operation of prejudice". This statement seems to disregard the possibility (raised by themselves a few paragraphs later) that prejudice would not necessarily be shown even if there "is scope for the operation of prejudice". In addition, one of the most important reasons for placebo controls is that they *always* provide a useful baseline for one component of the "placebo success rate", i.e., the spontaneous changes that occur over time independent of "suggestability" phenomena. Such spontaneous changes may be due to the natural history of the disease, changes in personnel and hospital procedures, etc.

The aim of the therapeutic trial is, of course, the accurate reporting of improvement or deterioration when it occurs. No control is a guarantee against over-reporting or under-reporting, e.g., a thoroughly negativistic observer can deny improvement in all patients regardless whether he knows what treatment they are on. Similarly, a "Pollyannaish" observer can blithely report improvement in all patients, regardless of what they are receiving, and come up with equally useless data, regardless of whether the trial is double blind or not. Most observers, fortunately, fall between these extremes, and it becomes important to eliminate to as great a degree as possible their temptation to be biased in one direction or another, and to dilute out this bias equally over treatment and non-treatment groups. When observers are not told which patients are on medication, they are always susceptible to a certain doubt: they know that all patients in the trial are not showing symptoms, and have no way of telling for certain whether those who show symptoms are getting a different preparation from those who do not. The result of this uncertainty is usually to provide a sufficient brake on their imaginations to diminish or prevent the "observing" of non-existent improvement and the denying of true improvement. (Observers also have no reason to expect that side effects must necessarily be shown by patients in order to show beneficial effects; in fact, they may be biased in the other direction, i.e., the occurrence of side effects may actually cause them to understate the presence of improvement. This latter possibility was not considered by Drs. LETEMENDIA and HARRIS and could theoretically negate the last statement in their paper to the effect that "final assessment of patients was not affected", although I do not believe this possibility to be an especially likely one.)

Actually, the results of the reported trial seem to demonstrate the pattern most commonly seen in drug studies; a) not all drug-treated patients showed side effects, b) some of the placebo-treated patients showed side effects, and c) there was no neat and tidy relationship between the occurrence of side effects and therapeutic change. It appears to this writer that the statement by Drs. LETEMENDIA and HARRIS that unless guesses are completely random the double blind procedure is "invalid" and "self-defeating" is an unfortunate one which will only supply grist for the mill of those less sophisticated observers who will seize on this paper as another demonstration of the "senselessness" of the double blind technique. In fact, the paper provides a strong argument for the very technique which its authors at least partially denigrate, and for which they provide no satisfactory substitute.

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Psychopharmacologia 1, 354—356 (1960)

Reply to L. Lasagna's Comments

By

F. J. J. Letemendia and A. D. Harris

(Received April 15, 1960)

Dr. Lasagna has raised several points of wide interest in his critique of our paper[1]. Before dealing with specific points of difference between us, we would like to comment on a general misapprehension that underlies his comments. This is, that we are taking sides in an all-or-nothing controversy for or against the double-blind trial. What we attempted to do was to study the mechanism of a double-blind trial, and we were led to advocate, first, that other empirical studies should be made (for we do not know how widely or narrowly our results may apply) and, secondly, that the double-blind method should be applied with greater discernment. Double-blind trials have many advantages, as have other forms of controlled trial. Any trial, even without control, may be useful if it is thoughtfully carried out. But no method obviates the need for evaluation of results, and comparison with those yielded by other methods.

The first point considered by Dr. Lasagna is our finding that somatic symptoms were reported by the nursing staff with greater frequency among patients who showed flushing than those who did not. In our paper we said that "it may be surmised that one effect of drugs which produce somatic side-effects is to cause increased attention to be paid to those patients who show these changes". Dr. Lasagna comments that "an alternative explanation is that those patients who demonstrate flushing are the patients most likely to report other side-effects". This is certainly an alternative explanation, but not, we think, a more likely one. The mechanism by which patients showing a noticeable physical sign may attract an undue share of the attention of the nursing staff is fairly straightforward: but the mechanism which Dr. Lasagna suggests may be operating is not at all clear. Why should patients who demonstrate flushing (an objective sign) be more prone to report side-effects? A more reasonable proposition would be that patients who *complain* of flushing are more likely to complain of other side-effects. This would indeed be an important consideration when dealing with neurotic patients with an abundance of somatic symptoms. But in this case, as we stressed in our paper, we were dealing with chronic psychotic

[1] Letemendia, F. J. J., and A. D. Harris: The Influence of Side-Effects on the Reporting of Symptoms. Psychopharmacologia 1, 39—47 (1959).

patients with little tendency to produce subjective complaints. To substantiate the point, we have re-examined our original data and find that of 78 reports by the nursing staff only 13 were based on statements by the patients: the remainder were observations of behaviour, e.g., noisiness, resistiveness, abusiveness, shouting, quietness. A further piece of evidence is that the increase in reporting did not occur until the patients had been receiving the drug for three weeks. This is surely difficult to explain on the hypothesis that symptoms were, in any sense, "patient derived". On our hypothesis, the delay is understandable; and we drew attention to the fact that it was at the same period of the trial that false positive reports of flushing began to be received.

Next, Dr. LASAGNA quotes from our paper that, "*if the observers guess correctly in every case*, the double blind procedure is then useless and provides no safeguard against the operation of prejudice". (Our italics.) He does not dispute this point, but refers instead to a later part of the paper where we say: "it does not of course follow, because there is scope for the operation of prejudice, that prejudice will necessarily be shown." There is, however, no discrepancy. To put the point concretely, it will still be true that the lock is broken, even if the burglars have not broken in.

In the same paragraph, he defends the double blind procedure, on general principles, that it provides a control on spontaneous changes not related to therapy. This, of course, is as true of any controlled trial as it is of the double blind variety. Continuing his argument, Dr. LASAGNA says that "no control is a guarantee against over-reporting or under-reporting", and adds that "most observers, fortunately, fall between these two extremes, and it becomes important to eliminate to as great a degree as possible their temptation to be biased in one direction or another, and to dilute out this bias *equally*." (Our italics.) This is precisely the point. But Dr. LASAGNA fails to say how we are to dilute out the bias equally or how we are to recognise whether we have done so. The assumption underlying the double blind technique is, as he remarks, that the dilution is equal — or, as we put it, that "guesses are randomly distributed". We pointed out in our paper that this assumption may be false. If it is, statements about the placebo group are invalidated to the same extent as those about the treated group.

Parenthetically, Dr. LASAGNA remarks that "observers also have no reason to expect that side effects must also be shown by patients in order to show beneficial effects. They may be biased in the other direction", and thus, he argues, the statement that the final assessment of the patients was not affected could be "theoretically negated". Presumably he means that the treated patients did really improve (an

eventuality which the experiment was designed to preclude), but because of the observers' negative bias this was not recognized. This could be validly argued only if our interpretation of the results is accepted, and then only by postulating two rather unlikely effects, equal in magnitude, but opposite in sign. We agree that this possibility is not "an especially likely one".

Dr. LASAGNA begins and ends his letter on a cautionary note. He feels that our "misleading statements may be misinterpreted by many readers" and "may supply grist to the mill of those less sophisticated observers who will seize on this paper as another demonstration of the 'senselessness' of the double blind technique". We have done our best with the statements which Dr. LASAGNA found misleading, but we cannot take all the blame for the misinterpretations which he foresees.

Dr. F. J. J. LETEMENDIA, Littlemore Hospital, Oxford/Great Britain

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